ARCHIVES OF SURGERY

VOLUME 35 NOVEMBER 1937 NUMBER 5

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INFLUENCE OF VENOUS STASIS ON THE PRODUCTION OF CHRONIC ARTHRITIS

PAUL E. McMASTER, M.D.
LOS ANGELES

Circulatory disturbances resulting from either experimentally produced venous stasis or obstruction of the arterial blood supply have been claimed to produce the changes of chronic arthritis. If venous stasis or passive congestion is capable of producing chronic arthritis, then the joints of the ankles and feet of persons with long-standing edema and stasis from varicose veins of the legs should show evidence of arthritis. In an effort to determine what effect if any venous stasis has clinically on the production of chronic arthritis, thirty cases of varicose veins of long standing in which definite and prolonged edema of the ankles and feet had existed were studied.

The patients in this group of cases presented histories of long-standing varicose veins of the legs with marked congestion of the ankles and feet associated with edema, cyanosis and occasionally eczematous changes of the skin, such as scaling and brownish discolorations. A palpable decrease in the cutaneous temperature of the feet was often present, and arterial pulsation of the dorsalis pedis and posterior tibial arteries was frequently diminished and in two cases was not obtainable. Some of the patients had ulcers of the legs of varying duration associated with the varicosities. The Wassermann reaction of the blood was negative in the cases in which ulceration was present.

Roentgenograms were made of the legs and feet. These were studied for signs of chronic arthritis, such as capsular thickening, marginal articular lipping, narrowing of the articular cartilage and subchondral sclerosis, and also for periosteal new bone formation of the tibia and fibula, especially in the cases of ulceration.

To be certain that the venous stasis did not merely involve the superficial soft parts without similarly affecting the deeper periarticular structures, tissue surrounding and including the joint capsules of the ankles and feet was obtained at autopsy in three cases of long-standing

From the Department of Surgery, Division of Orthopedics of the University of Southern California and the Los Angeles County General Hospital.

stasis associated with varicose veins. On gross examination this tissue appeared thickened, as from edema, and microscopically revealed evidence of edema, arterial thickening with some thrombosis and an increase in fibrosis.

Of the thirty patients studied, twenty-one were men and nine were women. The ages ranged from 29 to 83. Varicose veins had existed for from one to fifty years. Eighteen patients had either old healed

Fig. 1 (case 15).—Roentgenogram in a case of varicose veins of nine years' duration with ulceration. Marked periosteal new bone formation of the shafts of the tibia and the fibula is evident. Arthritic lipping of the astragalus (*A*) is noted in the lateral view.

varicose ulcers or ulcerous lesions on the legs when studied. There were five cases in which hypertrophic arthritis of joints other than those of the foot and ankle was demonstrated.

RESULTS OF STUDIES

In seven cases in which there were active ulcerous lesions overlying the lower part of the leg there was periosteal new bone formation involving either the tibia or the fibula or both. In addition to the

periostitis, in three of these seven cases there were arthritic changes in the joints of the foot and ankles (fig. 1).

There were nine cases among the thirty studied in which the necessary roentgenographic evidence was present to establish a diagnosis of chronic arthritis. In each of these there was an associated varicose ulcer, either active or healed and near the ankle joint. In one of these cases the patient had received a fracture of the tibia and fibula eleven years before. Varicosities and an ulcer distal to the site of the fracture

Fig. 2 (case 11).—Roentgenogram in a case of varicose veins of four and one-half years' duration with ulceration. An eleven year old healed fracture with angulation and poor weight-bearing alinement at the ankle joint is evident. The arthritic changes in the tarsal bones (*A*) were probably of "mechanical" origin.

developed subsequently. Roentgenograms of the foot revealed marked arthritic changes, most probably from an angulation at the site of the fracture which gave a poor weight-bearing alinement at the ankle joint (fig. 2).

In twenty-one cases there was no roentgenographic evidence of arthritis, even though in nine of these there were varicose ulcers. The results are shown in the accompanying table.

COMMENT

Chronic arthritis of the joints of the ankle or foot could not be demonstrated in twenty-one of the thirty cases of long-standing passive congestion of these parts resulting from varicose veins (fig. 3). In nine cases there was some evidence of arthritic changes, but in each there

Data in Thirty Cases of Long-Standing Venous Stasis Due to Varicose Ulcers

Case	Age	Sex	Leg or Legs Involved	Varicose Ulcer	Arthritis of Ankle or Foot Joint	Ossifying Periostitis	Duration, Years
1	65	M	Both	0	0	0	25
2	69	F	Left	Above ankle	Slight	0	5
3	64	F	Both	Large; healed	Slight	0	50
4	46	M	Both	+	0	0	2
5	45	M	Both	0	0	0	6
6	67	F	Both	0	0	0	Years
7	45	F	Both	0	0	0	Years
8	48	M	Both	Left	0	0	5
9	43	M	Both	Right	0	Tibia	2½
10	53	M	Both	Right ankle	+	0	26
11	56	M	Both	Old fracture; ulcer	+	Tibia and fibula	4½
12	83	M	Both	+	+	0	Many
13	46	M	Right	Right	0	0	1
14	29	M	Both	+	0	0	10
15	62	M	Left	+	+	Tibia and fibula	9
16	56	M	Both	+	+	Tibia and fibula	20
17	58	M	Left	+	0	0	4
18	39	M	Left	+	0	Tibia	15
19	59	M	Both	0	0	0	Few years
20	60	M	Both	0	0	0	6
21	48	M	Both	0	0	0	8
22	52	F	Both	Right ankle	+ (right)	0	Years
23	44	M	Both	+	0	Tibia and fibula	12
24	57	F	Right	Healed	+	0	25
25	32	M	Both	Left	0	0	12
26	32	F	Both	0	0	0	6
27	65	M	Both	Left	0	Fibula	Years
28	31	F	Both	0	0	0	2
29	40	F	Both	0	0	0	5
30	35	M	Both	0	0	0	8

was either an associated active or a healed ulcer in the region of the ankle point. In none of these cases were there marked changes in the joints except in the one in which there was an added "mechanical factor" from a poor weight-bearing alinement at the ankle joint due to malposition of a fractured tibia.

In one of the cases of most severe bilateral varicose veins, one of twenty-five years' duration with large ulcerous lesions over the lower third of the leg for several years and diffuse extensive edema of the foot and ankle, eczematous changes of the skin and cyanosis, only minor arthritic changes were observed (fig. 4).

Hence, in cases of marked venous stasis resulting from varicose veins, chronic arthritis did not develop unless there was an added element of ulcerous infection near the ankle joint, and then the changes were not of an advanced degree.

In studies on the circulation of the extremity with varicose veins, de Takáts and his co-workers [1] concluded that there is an increase in venous pressure with a resultant marked edema. In addition, they found that the carbon dioxide content of the blood of the varicose veins

Fig. 3 (case 7).—Roentgenogram showing no definite demonstrable arthritic changes in a case of varicose veins of many years' duration without ulceration.

of the leg is increased and the oxygen content is decreased. These workers also studied the histamine reaction of persons with varicose veins of the extremities and noted a delayed reaction or absence of reaction, suggesting an impaired arterial circulation to the part. They explained eczema and periosteal thickening as a result of the venous congestion.

1. de Takáts, G.; Quint, Harold; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

Bernstein [2] made experimental observations on the influence of venous stasis in the production of chronic arthritis by ligating the lumbar vertebral veins of dogs. He examined the lumbar vertebrae after two years and concluded that changes of chronic arthritis had occurred. The clinical observations outlined do not substantiate these experimental findings. In direct contrast to the work of Bernstein [2] are the observations of Goldhaft, Wright and Pemberton,[3] who demonstrated that obstruction of the arterial blood supply to the patella in dogs resulted in chronic arthritis. This work, they stated, verified the original and similar observations of Wollenberg [4] in 1909. Adson

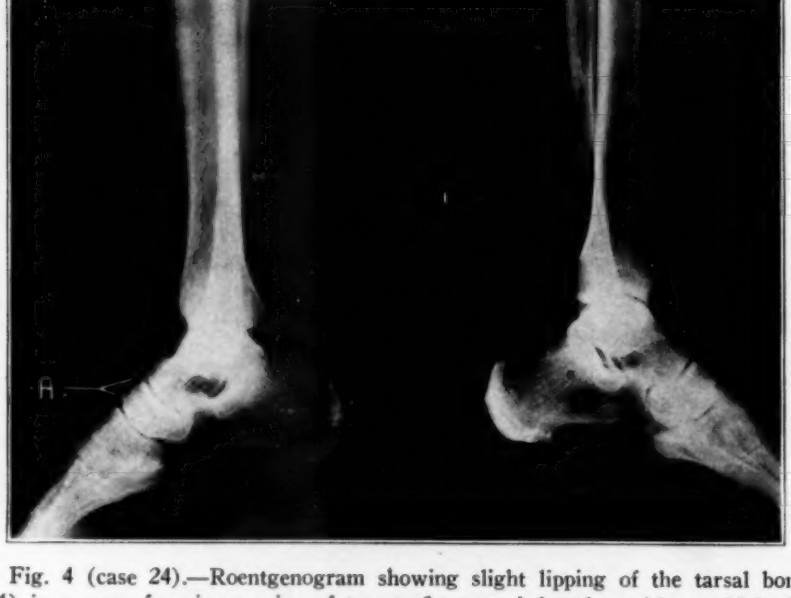

Fig. 4 (case 24).—Roentgenogram showing slight lipping of the tarsal bones (*A*) in a case of varicose veins of twenty-five years' duration with an old healed ulcer.

and Rowntree [5] assumed that the changes of chronic arthritis in younger persons are due to circulatory changes of a vasospastic type. This opinion was also expressed by Goldhaft, Wright and Pemberton.

2. Bernstein, M. A.: Experimental Production of Arthritis by Artificially Produced Passive Congestion, J. Bone & Joint Surg. **15**:661, 1933.

3. Goldhaft, A. D.; Wright, L. M., and Pemberton, R.: The Production of Hypertrophic Arthritis by Interference with the Blood Supply, Am. J. M. Sc. **180**:386, 1930.

4. Wollenberg, quoted by Goldhaft, Wright and Pemberton.[3]

5. Adson, A. W., and Rowntree, L. G.: The Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, Surg., Gynec. & Obst. **50**:204, 1930.

There is evidence to substantiate the statement that venous stasis hastens the repair of experimentally made bone defects (Pearse and Morton [6] and McMaster and Roome [7]). Harris [8] has shown that venous stasis resulting from various pathologic processes not uncommonly accelerates the growth of long bones in children. In these conditions, however, the venous stasis exerts an influence first on bone and periosteal elements stimulated to repair by trauma and secondly on immature cartilage and bone cell elements which are actively proliferating, and not on mature, relatively inactive cartilage and bone elements, as in these cases of varicose veins.

In discussing arthritis deformans (chronic arthritis), Lang [9] considered functional and mechanical trauma of the first importance. This is often noted clinically and is illustrated in figure 2.

Ossifying periostitis associated with long-standing varicose ulceration is often noted (Morris [10] and Kilbourne [11]). These changes are explainable on the basis of congestion plus infection and are well shown in figure 1. Somewhat similar changes in the bones of the forearm and leg are noted in secondary hypertrophic osteo-arthropathy. These changes, according to Locke [12] are due to two factors, namely, stasis and toxemia. The latter has its origin most often in some long-standing chronic pulmonary lesion. Locke [12] expressed the belief that occasionally in some cases of clubbing of the fingers and toes associated with ossifying periostitis of the long bones in which only a cardiac weakness exists stasis alone may account for the changes. Similar periosteal reactions were noted in the foregoing clinical cases in which stasis plus infection was present, but no periosteal new bone formation could be demonstrated in cases of venous congestion in which there was no associated infection.

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6. Pearse, H. E., Jr., and Morton, J. J.: The Influence of Alterations in the Circulation of the Repair of Bone, J. Bone & Joint Surg. **13**:68, 1931.

7. McMaster, P. E., and Roome, N. W.: The Effect of Sympathectomy and of Venous Stasis on Bone Repair, J. Bone & Joint Surg. **16**:365, 1934.

8. Harris, R. I.: The Effect of Lumbar Sympathectomy on the Growth of Legs Shortened from Anterior Poliomyelitis: A Preliminary Report, J. Bone & Joint Surg. **12**:859, 1930.

9. Lang, F. J.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, J. Bone & Joint Surg. **14**:563, 1932.

10. Morris, D. H.: The Deeper Structural Changes Arising from Varicose Ulceration, Surg., Gynec. & Obst. **30**:72, 1920.

11. Kilbourne, N. J.: Leg Ulcers of Unrecognized Etiology, J. A. M. A. **98**: 1955 (June 4) 1932.

12. Locke, E. A.: Secondary Hypertrophic Osteoarthropathy, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, London, Oxford University Press, 1921, vol. 4, pt. 2, p. 431.

SUMMARY

Chronic arthritis of the joints of the ankle or foot could not be demonstrated roentgenographically in twenty-one of thirty cases of long-standing passive congestion and edema of these parts resulting from nonulcerated varicose veins.

In nine of the thirty cases there was roentgenographic evidence of chronic arthritis of the joints of the ankle and foot, but in each there was associated ulceration of the leg or near the ankle joint in addition to the passive congestion from existing varicose veins.

Ossifying periostitis of either the tibia or the fibula or both did not occur from venous stasis alone but did occur in seven cases in which ulcerous lesions existed with the varicose veins.

FIBROBLASTIC TUMOR OF THE EXTREMITIES

EDGAR M. BICK, M.D.
NEW YORK

The fibroblastic tumor is among the most common of all the soft tissue tumors involving the extremities and is exceeded in number only by the benign lipoma. The tumor may originate from any area in the connective tissue stroma of the limb and therefore may be found attached to, or growing within, any of its special structures. Fibroblastic tumors range in degree of malignancy from the questionably neoplastic fibrous nodule, which arises as a reparative reaction to local irritation, to the malignant fibrosarcoma. However, such tumors, regardless of form or area of origin, present a clinical and pathologic similarity which justifies their inclusion in a single group. It is partly the object of this paper to demonstrate this fact and to demarcate the group of tumors to which it applies. Before entering into a discussion of their special characteristics, it is necessary that a clear definition of terms be given. A fibroblastic tumor is a neoplasm of mesodermal origin, composed of cells the ultimate function of which is the production of fibrous connective tissue. Such tumors vary within the limits of precursing tissue structure and of adult connective tissue variations. Two factors have tended to obscure the recognition of fibroblastic tumors of the extremities: First, fibroblastic tissue, being a component of almost every tissue of the extremity, may be found in greater or lesser quantity in almost every neoplasm of this region. Second, the earlier the developmental stage of the tissues comprising any of several mesodermal tumors, the more closely do they resemble each other in histologic appearance. It is essential that the variations to which the true fibroblastic tumors are subject be clearly recognized. Knowledge of the path of development (table 1) of the various types of adult connective tissue (table 2) is elementary but fundamental to a proper understanding of this group.

In the components of the fibroblastic tumor no cellular structure is recognized below the mesenchymal, and this only in its later stages, bordering on embryonal connective tissue. The structure of the tumor

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Read before the New York Academy of Medcine, Section of Orthopedic Surgery, Oct. 16, 1936.

From the Hospital for Joint Diseases (Service of Dr. S. Kleinberg) and the Orthopedic Service of Mount Sinai Hospital.

is characterized by the presence of typical stellate cells embedded in a homogeneous fluid matrix. In a more advanced state mucoid substances appear in the matrix, giving certain microchemical stain reactions, which are recognized as specific for myxomatous tissue. At a still later stage the myxomatous tissue disappears, and the adult fibroblastic cell appears, the chief function of which is to produce and / or support "collagen and argyrophile fibers."[1] This adult cell is the typical spindle cell of fibrosarcoma. In the adult stage connective

TABLE 1.—*Development of Connective Tissue*

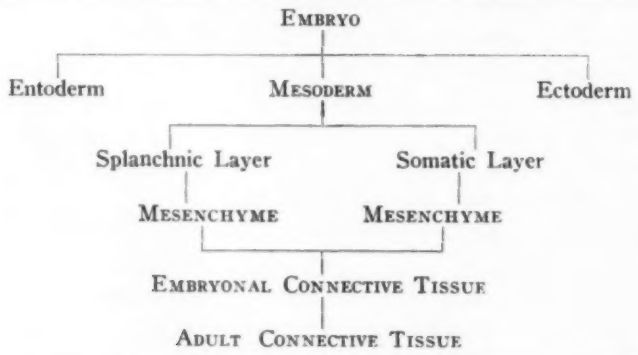


TABLE 2.—*Variations in Adult Connective Tissue*

Adult Connective Tissue	Embryonal *	
	Reticular	
	Fibrillar	Areolar
		Dense fibrous
		Elastic

* Embryonal connective tissue is not found normally in the adult but appears during connective tissue repair and neoplasia.

tissue varies normally in the density of its cellular and fibrous structures, in its vascular and adipose tissue content and in the quality and quantity of its wandering tissue cells. These variations are conditioned by the demands of regional structure and function.

In summary, a fibroblastic tissue tumor is defined and qualified by the fact that its predominant cell possesses the property of forming fibrous tissue. The tumor may present the structure of this tissue in any form from its adult stage to any of its precursing stages. For the benign form of tumor common usage has retained the name fibroma, but for the malignant form there has been confusion owing to a super-

1. Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932.

fluity of names. Among these are sarcoma, spindle cell sarcoma, round cell sarcoma, oat cell sarcoma and pleomorphous cell sarcoma, fibroblastic cell sarcoma and fibrosarcoma. The last two terms most suitably define the tumor, and since fibrosarcoma is less cumbersome it is herein adopted, and its general use is urged. The other terms merely describe structural variations in an identical tissue and serve unnecessarily to confuse a specific clinical entity.

It must be noted at this point, however, that myxomatous tissue is not only associated with the fibroblastic tumor but may appear alone or as a part of any neoplasm of mesodermal origin. Furthermore, the developmental concept of oncology does not imply that every fibroblastic neoplasm must pass through a myxomatous stage before becoming predominantly fibrous. The nature of the tissue structure of a given tumor depends on the degree of differentiation of its cells at the time of active proliferation. In a number of cases in my collection specimens were taken from recurrent growths. I have never observed a change in the quality of cell structure in a fibroblastic tumor, although I have observed changes in the quantity or density of the cellular content.

RELATIVE FREQUENCY

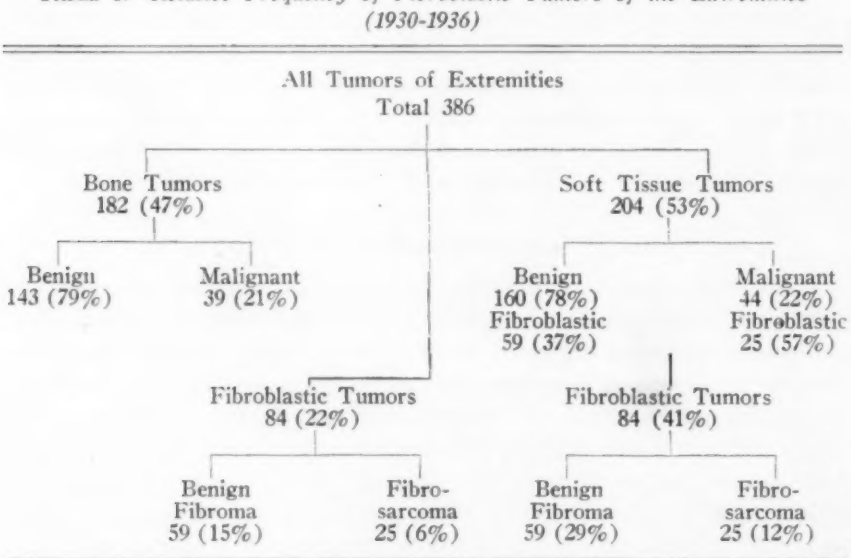
Regrettably, the literature gives no idea of the relative frequency of fibroblastic tumors of the extremities. Valuable reports of fibrosarcoma are usually based on series of from 5 to 19 cases. Papers reporting therapeutic results in large groups (up to 678 cases) do not designate the specific character of the sarcomas examined, and as the complex family of soft tissue sarcoma embraces a wide assortment of tumors, such studies are of little help. Recently I attempted to determine within a reasonable margin of error the actual and the relative frequency of fibroblastic tumors of the extremities. For this purpose the diagnostic files of the Hospital for Joint Diseases from 1930 to 1935 inclusive were consulted. The diagnoses for these files were copied from the pathologists's report in all cases of tumor in which operation or biopsy was done, and clinical diagnoses were used only in the cases of inoperable tumor or in those cases in which for some other reason operation was not performed. The last two groups form a small proportion of the cases of tumor seen at the hospital. No cases are included in which the diagnosis was made in the outpatient department. The relative figures, based on this list, are given in table 3.

In actual frequency, 84 fibroblastic tumors of the extremities were seen in the various services of the Hospital for Joint Diseases from 1930 to 1936. This represented 22 per cent of all tumors of the extremities seen within that period and 41 per cent of the soft tissue tumors of the extremities.

SURGICAL PATHOLOGY

Since the diagnosis of any tumor depends on the interpretation of histologic material, it is incumbent on the surgeon who deals with a growth to have a reasonable knowledge of its pathologic structure. The morphologic picture of a typical fibroblastic tumor is characteristic. There is a proliferation of cells in a connective tissue stroma, with a coincident increase in fibers. Where the neoplasia of spindle-shaped fibroblasts is visibly evident, the commonly used hematoxylin-eosin stain may suffice for diagnosis. However, in those fibroblastic tumors in which the cells are immature or in which the histologic field

TABLE 3.—*Relative Frequency of Fibroblastic Tumors of the Extremities (1930-1936)*



does not conform to that of the typical specimen, purely cytologic study may be insufficient. One or more of several special tissue stains will then demonstrate the presence of excessive fiber formation and the relationship between fiber and cell content or between the predominant neoplastic cell and its host tissue. The Van Gieson and the Mallory stain for connective tissue and the Laidlaw stain for silver-negative fibroblastic cells are among the more common of these differential stains. The first two stains are well known.[2] They serve to disclose the presence of fibers within the stained field and are most useful in defining fibroblastic tumors of the adult cell type. The Laidlaw silver

2. Laidlaw, G. F.: Silver Staining of the Skin and of Its Tumors, Am. J. Path. **5**:239, 1929; in Stout.[1]

stain finds its most valuable application among fibroblastic tumors when the cells are of the immature type, that is, when the cells are not characteristically spindle shaped.

A difficult complication in the study of the fibroblastic tumor is the fact that the growth may arise from within or invade other special tissues, such as fat, bone, muscle, nerve sheaths or the walls of blood vessels. Whether or not a given tumor containing adipose and fibrous tissue or muscle fibers and connective tissue is a fibroblastic tumor may sometimes be a matter of judgment rather than a matter of fact. Judgment in these cases can be confirmed only by the subsequent history of the tumor. Fortunately, these instances are relatively rare, and more extensive use of differential stain technic will decrease their number still further. The presence of an abundant vascular tissue in a connective tissue neoplasm requires special consideration. Such tumors have been classified as angiosarcoma. Livingstone and Klemperer in 1926 discussed this type of tumor under the term malignant angioma.[3] They pointed out that the name was misleading and that the neoplasm showed merely the "simultaneous presence of undifferentiated mesenchymal and angiomatous structures in a malignant tumor." Stout agreed that the term angiosarcoma should be dispensed with, since the tumor in question is either a malignant angioma in a fibroblastic matrix or a highly vascular fibrosarcoma. From the reported cases and from the cases presented here, there is no evidence that the vascularity of a fibroblastic tumor influences its degree of malignancy. A benign fibroma may present a relatively extensive vascular invasion, as in 1 of my cases in which the tumor had remained static for about fifteen years before an acceleration of growth invited surgical removal. On the other hand, I have listed in my series of cases 1 in which a vascular fibroblastic tumor of the deltoid region was excised in 1932 and recurred within a year. In reviewing the material there is no morphologic indication which even in retrospect would associate the grade of malignancy with the extent of vascularity. These tumors acted clinically in a manner characteristic of fibroblastic tumors.

One of the most confusing diagnoses in the field of oncology has been that of neurofibrosarcoma, or neurogenic sarcoma. The work of Masson[4] and the recent studies of Stout[5] and Foot[6] have helped

3. Livingston, S. F., and Klemperer, P.: Malignant Angiomas, Arch. Path. **1**:899 (June) 1926.

4. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), Am. J. Path. **8**:367 and 389, 1932.

5. Stout, A. P.: Malignant Tumors of the Peripheral Nerves, Am. J. Cancer **25**:1, 1935.

6. Foot, N. C.: Peripheral Neurogenic Tumor, Am. J. Clin. Path. **6**:1, 1936.

greatly to clarify this obscure problem. There can be differentiated from the general group of tumors of the peripheral nerves a true fibroblastic sarcoma arising from the connective tissues of the nerve sheaths. Because of its association with neurogenic tissues, histologic sections may include areas showing nerve fibers, or schwannian elements, but the predominant neoplasia is seen to be among fibroblastic cells. A fibroblastic tumor derived from this source often is associated with the generalized neurofibromatosis of Recklinghausen. It is more likely to be encapsulated than are similar tumors derived from other sources. I have indicated in a previous publication that a fibroblastic tumor of nerve sheath origin frequently remains static over a long period before showing a renewed acceleration of growth.[7] However, this observation is in all probability related to the tendency toward the formation of a capsule. Late increase in the rate of growth may occur in any fibroblastic tumor, even in the absence of a demonstrable capsule.

A fibrosarcoma arising from the outer layer of periosteum may either grow away from the bone or invade its substance. In the former case, that of the so-called parosteal or periosteal fibrosarcoma, the bone may be surrounded by tumor tissue, with possibly some superficial erosion of the cortex. If the tumor invades the bone it is usually diagnosed both by roentgenographic and by clinical examination as a bone tumor. I have several such cases in which the iliac bones are involved. However, histologic study in these cases shows a pure fibroblastic tumor with no signs of bone formation. Geschickter has reported a series of cases in which fibrosarcoma invading bone substance arose not only from the outer layer of the periosteum but from adjacent soft tissues.[8] In so-called fibroliposarcoma or the benign form, fibrolipoma, a similar approach will simplify the problem. If excessive fibrillar proliferation is present in an adipose field, the diagnosis of fibroma or fibrosarcoma is warranted. If there is an obvious proliferation of fatty tissue and only a normal amount of fibrous tissue is present in the stroma, the growth is a lipoma or a liposarcoma. It should not be forgotten in this connection that the fibrous content of adipose tissue varies in different regions of the body. Only in those specimens in which there is simultaneous neoplasia of fatty tissue and fibroblastic tissue can the use of the term fibrolipoma or fibroliposarcoma be justified. The developmental or embryologic relationship between these two mesodermal derivatives is common knowledge. However, at the stage of tumor formation their differentiation has become too far advanced for metaplasia.

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7. Bick, E. M.: Fibrosarcoma of the Extremities, Ann. Surg. **101**:759, 1935.

8. Geschickter, G. F.: So-Called Fibrosarcoma of Bone: Bone Involvement by Sarcoma of Neighboring Soft Parts, Arch. Surg. **24**:231 (Feb.) 1932.

The significance of myxomatous tissue in a fibroblastic tumor was discussed previously. The presence of mucoid substance as demonstrated by the mucicarmine stain determines its diagnosis and differentiates it from the more common and often mistaken edema of simple fibrous tissue. Thibaudeau and Kress [9] have published one of the most complete studies of myxomatous tumors in recent years. Their report is based on a study of 51 tumors which these authors grouped as follows: 9 as myxofibroma, 39 as myxosarcoma and 3 as myxoliposarcoma. Approached from my point of view, 48 of the 51 were fibroblastic tumors and 39 were malignant. The authors stated:

> An attempt was made to correlate the histological appearance of the growth with the clinical course of the disease, but we were unable to determine that any histological feature observed in our sections could aid us in determining the degree of clinical malignancy. We did observe, however, that those tumors in which mitosis was most marked were as a rule most rapidly fatal.

In my own collection of tumors I have thus far 6 fibroblastic tumors of the extremities exhibiting areas of myxomatous tissue. The ages of the patients varied from 24 to 60; 4 of the 6 tumors occurred on the thigh. This is entirely in accord with the larger series of cases reported by Thibaudeau and Kress. I am in entire agreement with their views on the inadequacy of histologic interpretation of the degree of malignancy; furthermore, I do not believe that the presence of myxomatous tissue in any way influences the prognosis of the tumor as compared with fibroblastic tumor which does not contain demonstrable myxomatous tissue.

The presence of muscle fibers in a tumor of the extremities demands clear oncologic differentiation. One must first distinguish between tumors composed of true myoblastic elements, such as myoblastoma or rhabdomyoma, and those derived from associated tissues which in the course of neoplasia have infiltrated the fascicles of the muscles.[10] That the fibrosarcoma is the most common of all tumors of skeletal muscle was shown by me in 1934.[11] Of 35 unselected tumors involving skeletal muscle reports of which were collected at that time, 50 per cent were fibroblastic. The extensive distribution of connective tissue surrounding and within muscle substance offers a wide surface area for the inception of fibroblastic neoplasia. The clinical data collected concerning fibroblastic tumors of skeletal muscle differed in no way from those concerning fibroblastic tumors of other tissue origin in the extremity, and here, too, the presence of an associated tissue did not change the general rate of growth, recurrence or metastasis.

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9. Thibaudeau, A. A., and Kress, L. C.: Myxosarcomata, Am. J. Cancer **23**:267, 1935.

10. Klemperer, P.: Myoblastoma of the Striated Muscle, Am. J. Cancer **20**: 324, 1934.

11. Bick, E. M.: Skeletal Muscle Sarcoma, Ann. Surg. **99**:949, 1934.

CLINICAL OBSERVATIONS

In considering fibroblastic tumors of the extremities as a specific group, certain repeated observations become emphatic. For the most part, their natural history runs to a true form with few modifying exceptions. Encapsulation is found more frequently in fibrosarcomas derived from nerve sheaths and probably related to this is the tendency of this type of tumor to remain static for long periods of time before showing progressive growth. As a group, even without these exceptions, fibroblastic tumors vary greatly in malignancy. The diagnosis of benign fibroma is not a factual statment; it is an interpretation of histologic appearance and must be so regarded. A fibroma is benign only when after years of follow-up study there has been no recurrence. A true fibroma, no matter how casual its clinical or histologic appearance, must be considered a potential fibrosarcoma until its benignity is established by its subsequent behavior. Except for the general proposition that cellular tissues are more likely to be rapidly malignant than are relatively acellular tissues, I have not been able to establish any correlation between the histologic structure of a fibroblastic tumor and its relative malignancy.

The average period of time between the first recognition of tumor and death in the fatal cases was between two and three years, and all but a few of the patients died within that period. In 14 cases of fibrosarcoma in which the condition has not yet proved fatal and in which excision or excision plus irradiation was the treatment employed, recurrence was found to take place as follows:

Case No.	No. of Recurrences	Time After Operation, Yr.
1	2	2.0
2	1	1.0
3	1	0.5
4	1	1.0
5	1	0.8
6	1	0.5
7	2	2.0
8	4	3.0
9	2	2.0
10	2	2.0
11	1	4.0
12	1	1.0
13	3	4.0
14	1	2.0

These figures cannot be converted into statistically significant averages. However, in general, they indicate that the expectancy of recurrence is highest in the first postoperative year and precipitately

decreases after that. In other words, if a fibroblastic tumor will recur, it will most likely do so within the first year; the probability of benignity is very high after that period if recurrence has not taken place. The clinical application of this is important. After the removal of an apparently benign fibroma, a follow-up period of one year is reasonably sufficient if no recurrence has taken place. However, when a recurrent growth has been excised, secondary recurrence appears, if at all, in less time than did the first. The acceleration of recurrence increases with each excision. In my series of cases the addition of irradiation to the treatment of a recurrent growth has not seemed to influence this fact. I can find no evidence in my cases to maintain the often-repeated hypothesis that all recurrent tumors are more cellular than are the primary specimens. Some are, and some are not. The rapidity of clinical recurrence is the only important criterion of the grade of malignancy of any given neoplasm.

Clinical observations on fibroblastic tumors of the extremities present a fairly uniform picture, regardless of their associated tissues or structures. I have found no significant sex distribution. In one of my series,[7] 25 cases occurred in males and 17 in females; in another somewhat overlapping series the sex distribution in 46 cases was exactly equal. It must be noted here, however, that a recent author reporting a similar series found the proportion to be in the neighborhood of 2:1, favoring males.[12] By considering the cases in both series, one might assume that fibroblastic tumors of the extremities are somewhat more common in males. Fibroma of the extremities occurs with almost equal frequency in each age group up to 50 years. The malignant form may appear at any age but is most common during the fourth and fifth decades. Sixty-four per cent of the fibromas in my series occurred in the upper extremity and 36 per cent in the lower. In both instances, about 80 per cent were found in the distal portions of the limbs, that is, on the hands and fingers or on the feet and toes. In these areas the most frequent host tissue was the tendon sheath. However, fibroblastic tumors involving the tendon sheaths of the distal segments of the limb represented only a small proportion of the malignant growths. Statistically, there appears to be some inexplicable predilection of certain parts of the limb for the malignant form of fibroblastic tumor. About 50 per cent of my series of fibrosarcomas of the extremities occurred in the thigh, and almost all of these involved the lower two-thirds. Of fibrosarcomas found on the upper extremity, about one half involved the forearm. Whether the relatively high

12. Meyerding, H. W.; Broders, A. C., and Hargrave, R. L.: Clinical Aspects of Fibrosarcoma of the Soft Tissues of the Extremities, Surg., Gynec. & Obst. **62**:1010, 1936.

degree of musculofascial stress and strain centered in these regions is significant or not is conjectural. However, the common distribution of fibrosarcoma at these segments is a valuable differential suggestion and distinguishes the growth from the more common benign lipoma, which occurs so predominantly about the shoulder and in the gluteal regions.[13] Pain is rarely of diagnostic or prognostic significance. It is almost never severe; considerable tumefaction may be present with relatively moderate discomfort. Radiation of pain along a nerve suggests only proximity or anatomic involvement of that nerve and is of no special importance. A fibroblastic tumor has a characteristic firmness on palpation. It is not as "stony hard" as most carcinomatous nodules or as soft as most lipomas. Mobility of the tumor depends on the tissue of origin. Fibromas vary in size from that of a pea to that of an egg. However, the smallness of a fibroblastic tumor is no indication of its innocence, since I have repeatedly seen a small nodule which was treated as a benign fibroma recur with a considerable degree of malignancy. A primary fibroblastic tumor of the extremity larger than an average-sized walnut has almost invariably proved to be a fibrosarcoma.

The tendency of fibrosarcoma is to grow by expansion rather than by infiltration. Ewing pointed out the propensity of this growth for following the paths of nearby blood vessels.[14] This leads to early invasion of the vascular system and hence in metastasis to direct involvement of the lungs and abdominal viscera. In fibrosarcoma of the extremities the regional lymph nodes are never involved, unless by direct extension from neighboring structures. Conversely, regional involvement of the lymph nodes is presumptive evidence against this neoplasm.[7] In my cases metastasis has occurred between two and four years after the original appearance of the tumor. However, the time of metastasis is unquestionably influenced by the treatment employed.

TREATMENT

The treatment of fibroblastic tumor of the extremities must be discussed with the greatest restraint. Reports in the literature vary considerably, and in most instances they consider a multiplicity of therapeutic measures, which confuses the results. For example, the method of multiple excisions with irradiation and final amputation is difficult to evaluate. The possibility of local excision acting as a stimulant to neoplasia, together with variations in the technic of irradiation used in the past twenty years, casts doubt on the virulence of a primary

13. Bick, E. M.: Lipoma of the Extremities, Ann. Surg. **104**:139, 1936.

14. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

malignant growth. Of even greater importance is the change in diagnostic concept concerning such tumors. Up to the period from 1925 to 1930, the term sarcoma as applied to soft tissue tumors was almost generic for all malignant tumors other than carcinoma. During this period, under the influence of Ewing,[14] Quick and Cutler[15] and Lewis and Hart,[16] many reports included rather benign neurogenic tumors under the category of sarcoma of the nerve sheath. In the absence of definite diagnostic criteria an evaluation of end-results is futile. A number of reports will demonstrate the variations encountered. Wollner[17] (1926) reported cures in 12.8 per cent of 39 cases of tumor in the advanced stage after surgical treatment and irradiation and in 28.5 per cent of 21 cases in the early stage after surgical treatment alone; De Waard[18] (1927) reported cures in 14 per cent of 74 cases after surgical treatment, and Rostock[19] (1928, in 6 per cent of 35 cases of inoperable tumor after irradiation alone, in 10.5 per cent of 38 cases of "borderline" tumors after incomplete surgical removal and postoperative irradiation and in 37 per cent of 46 cases of operable tumor after excision and irradiation. Hintze[20] (1930), in a report on 678 cases studied five years or longer, stated that cures were obtained in 28.7 per cent of 216 cases by surgical methods, in 39 per cent of 79 cases of recurrent tumors by irradiation, in 39 per cent of 82 cases by surgical methods and irradiation and in 24.9 per cent of 201 cases of inoperable tumor by irradiation. However, this series, even though grouped under the title of sarcoma, included growths which obviously would not today be so classified. Meves[21] (1931) reported cures in 11 per cent of 173 cases and also included cases in which the results were doubtful. The wide variation in percentage of cures, the tendency to broad use of the term sarcoma and the antiquity of many of the case records make judgment extremely difficult. Of more interest is a group of recent reports in the American literature. Pelletier[22] has

15. Quick, D., and Cutler, M.: Neurogenic Sarcoma, Ann. Surg. **86**:810, 1927.

16. Lewis, D., and Hart, D.: Tumors of Peripheral Nerves, Ann. Surg. **92**: 961, 1930.

17. Wollner, W.: Ergebnis einer 10 jährigen Sarkombehandlung, Beitr. z. klin. Chir. **138**:39, 1926.

18. de Waard, T.: Ueber Sarkome und die Resultate der chirurgischen Behandlung, Nederl. tijdschr. v. geneesk. **1**:822, 1927.

19. Rostock, P.: Indikationsstellung und Dauererfolg der Röntgenbestrahlung bei Sarkomen, Fortschr. d. Therap. **4**:241 (April 25) 1928.

20. Hintze, A.: Die Erfolge der operativen und der Bestrahlungsbehandlung beim Sarkom, Arch. f. klin. Chir. **162**:345, 1930.

21. Meves, F.: Der Erfolg der Sarkomtherapie in der Kieler chirurgischen Klinik (1914-1928), Deutsche Ztschr. f. Chir. **231**:691, 1931.

22. Pelletier, V. A.: Sarcomas, Am. J. Cancer **15**:2418, 1931; (supp.) **21**: 658, 1934.

been reporting small series of cases of fibroblastic tumor from the Pondville Hospital in which a careful follow-up study was made. The results have not been encouraging. In several cases in which it has been five years since treatment, recurrences appeared later in spite of adequate roentgen therapy. French [23] (1932) published a valuable series of end-results in 16 cases of fibrosarcoma, in 8 of which the growth involved the extremities. One patient with a fibrosarcoma of the thigh was well six years after amputation of the tumor, which had been present six months. One patient was well two years after amputation. The other patients, on whom amputation had not been performed, either died or had a recurrence. (One case was too recent for the results to be evaluated.) Leucutia [24] (1935) reported survivals of from five to twelve years in 34 per cent of 101 cases of sarcoma of the soft parts in which high voltage roentgen therapy and surgical measures were employed. However, he defined fibroblastic sarcoma as "all those sarcomatous tumors of soft-parts which cannot be placed in any of the well-characterized subgroups." I cannot consider that definition tenable, since it permits too great a latitude in diagnosis. Meyerding, Broders and Hargrave [12] (1936) reported end-results on 132 patients treated at the Mayo Clinic for fibrosarcoma of the extremities. Their figures are as follows: Twenty-one per cent lived for three years after excision or amputation; 17.5 per cent, from five to twenty years; 14.4 per cent, from five to ten years, and 6 per cent, from ten to twenty years.

The great variation in the percentages of reported cures is obvious at a glance and indicates the need for further investigation. From my own series there are not as yet sufficient follow-up data on properly controlled cases to offer a final therapeutic point of view. It has been necessary first to restudy the groups of tumors and to establish clinical and pathologic criteria for control study. However, during the course of this work certain therapeutic observations have become increasingly conspicuous. In general, they tend to agree with the observations in reports such as those of French and Pelletier, in which the results of a careful follow-up study over a period of time in individual cases and a study of adequate histologic material are presented. Of 9 patients with proved fibrosarcoma of the extremities, only 2 are living after five years. In 1 the tumor involved the connective tissue of the knee joint, and an amputation was performed at the time of the first recurrence. In the other, the tumor involved the region of the shoulder and was treated by excision and high voltage roentgen therapy, with no recurrence. A third patient with a tumor involving the thigh is alive

23. French, R. W.: End-Results in a Series of Sixteen Cases of Fibrosarcoma, New England J. Med. **206**:393 (Feb. 25) 1932.

24. Leucutia, T.: Radiotherapy of Sarcoma of the Soft Parts, Radiology **25**: 403, 1935.

four years after excision plus high voltage roentgen therapy; a fourth is alive three years after simple excision. All other patients, 5 in number, died of metastases after two or more recurrent tumors were excised or after a second or third recurrent tumor was amputated. These figures, combined with those of other authors reporting individual cases, suggest the following therapeutic indications. Since the malignancy of a primary fibroblastic tumor cannot as yet be judged by histologic study and since few, if any, such tumors metastasize before at least one recurrence, adequate excision, with or without high voltage roentgen irradiation, is the treatment of choice. The experience of several authors, including myself, has shown cures five years after this procedure. However, recurrence must be an indication for amputation. I have no case as yet, and few have been reported, in which five year cures are recorded after repeated excisions of recurrences. Whether present experiments with changes in the technic of irradiation will alter this rule in the future remains to be seen, but until well controlled end-results are shown irradiation for fibroblastic tumors cannot be depended on.

Dr. Paul Klemperer, of the Department of Pathology of Mount Sinai Hospital, and Dr. H. L. Jaffe, pathologist to the Hospital for Joint Diseases, rendered invaluable assistance in the study of this material.

EXPERIMENTAL GIANT CELL TUMOR AND CARTILAGINOUS EXOSTOSIS OF BONE

J. DEWEY BISGARD, M.D.
OMAHA

Incidental to the course of an investigation of an entirely unrelated problem there developed in several rabbits lesions of bone with all the characteristics of cartilaginous exostosis and in two rabbits tumors apparently identical to the giant cell tumor of man. These observations are reported because it is believed that they contribute some information relative to the etiology of these tumors.

The studies were made on fourteen immature rabbits from 1 to 3 months of age. In each a segment measuring approximately 20 mm. was removed from the shaft of the radius on both sides in block resections. In each animal the gap on the right side was bridged with an autogenous transplant of costal cartilage equal in length to the segment of bone removed, and on the left side it was left empty to fill with blood. The results of the original problem, which had for its purpose a comparative study of the repair of the radial defects with and without transplanted cartilage, will be published later.

Since no dressings were applied to the legs and the animals were compelled to bear weight immediately without support, and since the animals were immature, roentgenograms made on the day after operation revealed certain unanticipated complications and findings.

CARTILAGINOUS EXOSTOSIS

It was found that in twelve of the twenty-eight legs that were operated on partial or complete separation and displacement of the distal epiphysis of the ulna had taken place, presumably as the result of one or all of three factors: the prying against the shaft of the ulna at the time of operation, the bending stress of muscular pull and the torsion of weight bearing. Roentgenograms made two, four, eight and twelve weeks later demonstrated, strangely enough, either complete (in seven ulnas) or nearly complete (in five ulnas) spontaneous replacement of the epiphyses. In five of those which were completely reduced, longitudinal growth of each ulna was resumed and progressed normally, and no abnormalities developed. In the remaining seven there were definite disturbances of growth, including both deviation to the side

From the Departments of Physiology and Surgery, University of Nebraska School of Medicine.

Read before the Section on Orthopedic Surgery at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1937.

from the normal long axis and retardation of growth in length. Also there developed on the external surfaces of these seven ulnas projecting tumors which grossly and histologically were similar if not identical to the osteochondroma or cartilaginous exostosis observed in man. Two of the tumors were composed entirely of bone and apparently were simple osteomas. The other five were made up of bone which was continuous with the shaft. The outer convex surface of each tumor was covered with a layer of dense connective tissue, beneath which there was a layer of hyaline cartilage, which varied in thickness in different areas, as illustrated in figure 5 *A*. In the deeper layers of this cartilage the cells were arranged irregularly in rows, as in the epiphysial cartilage. In this zone, as shown in figure 5 *B*, the cartilage was undergoing calcification and was continuous with the deeper core of laminated spicules of bone which made up the bulk of the tumor. In the superficial layers

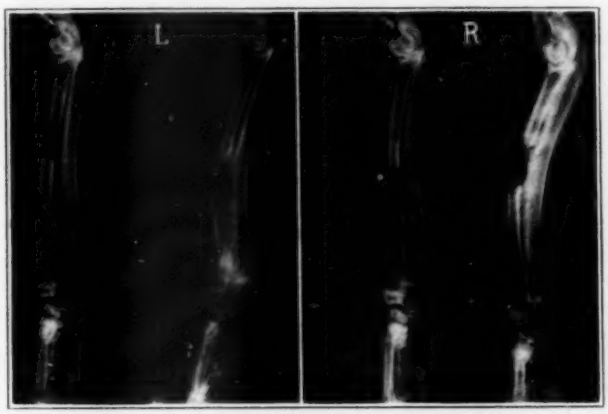

Fig. 1.—Serial roentgenograms of rabbit 9. On the left side of each pair of roentgenograms is shown complete separation of the distal epiphysis of each ulna immediately after resection of a segment of the shaft of each radius. There was complete and spontaneous reduction of these fracture dislocations, as shown in the roentgenograms on the right taken four weeks later. The right ulna resumed normal growth, and a cartilaginous exostosis developed in the left.

of bone there were several small islands of cartilage. The marrow between the bony trabeculae was sparsely cellular and mainly fatty. At the base of the tumor, on its proximal surface, the dense bone of the cortex extended up onto the tumor, having in this area no cap of cartilage.

As one studies the serial roentgenograms of some of these animals it is possible to build the progressive steps in the evolution of these tumors. Roentgenograms of rabbit 9 (fig. 1) made the day after operation showed complete separation and displacement of both ulnar epiphyses, and those made four weeks later showed spontaneous replace-

ment with no disturbance in the right leg but with the formation of a cartilaginous exostosis and a disturbance of growth in the left ulna. In this instance the tumor appeared to be continuous with the epiphysial cartilage at its distal margin.

In rabbit 4 (fig. 2) there was partial slipping of both ulnar epiphyses, which twelve weeks later resulted in retardation of longitudinal growth but no other abnormality.

In rabbit 8 (fig. 3) both ulnar epiphyses became completely separated and displaced and subsequently became partially replaced. There developed as a result fusion of the epiphysis with the diaphysis and complete arrest of longitudinal growth in the distal ends of both ulnas. In the left one (fig. 3 *A*) there formed a lobulated cartilaginous exostosis, and in the right one, a giant cell tumor, which will be discussed later.

Fig. 2.—Roentgenograms showing slipping with only partial displacement of both distal ulnar epiphyses with subsequent spontaneous reduction and retarded longitudinal growth. No exostosis developed.

In rabbit 3 (fig. 4) the steps in the formation of the cartilaginous exostosis were more clearly demonstrated. Both ulnar epiphyses slipped and subsequently became only partially replaced. The displaced lateral portion of the diaphysis, which normally approximated the epiphysis, was left free to project as a spur as the epiphysis moved distally away from it with continued longitudinal growth.

The histologic structure of these tumors is shown in figure 5.

From these observations, I have made the following deductions. The cartilage which formed a cap over the surface of each tumor was derived from, or was a portion of, the epiphysial cartilage. As separation of the epiphysis occurred, a portion or layer of the cartilage plate

remained adherent to the projecting edge of the distal end of the diaphysis. It became isolated from the rest of the cartilage, which moved distally away from it in the course of normal longitudinal growth. This isolated cartilage proliferated and continued to lay down bone, which explains the obvious rapid increase in size. As further evidence that the cartilage was derived from the epiphysial disk is the histologic similarity (the row formation of cells) and the appearance in one

Fig. 3.—*A*, roentgenograms of the left forearm of a rabbit taken immediately after operation and four and twelve weeks later. Note that as a result of epiphysial separation a lobulated cartilaginous exostosis developed in the distal end of the shaft of the ulna. *B*, roentgenograms of the right forearm of the same animal. Note the area of rarefaction in the bulbous distal end of the shaft of the right ulna in the film taken twelve weeks after operation. This contained a giant cell tumor.

specimen of continuity between them, suggesting that the displaced segment of epiphysial cartilage had not become completely detached and isolated.

COMMENT ON CARTILAGINOUS EXOSTOSIS

As a result of traumatic epiphysial separation and displacement, there developed in a series of rabbits tumors at the distal diaphysial ends of the ulnas. These tumors had the gross and the histologic appearance of cartilaginous exostoses in man; so it is suggested that some of these tumors in man (particularly the solitary ones) may have a similar etiology. In clinical cases an antecedent history of trauma is not infrequently obtained. It is possible that a segment of epiphysial cartilage from the border of the ulna may be displaced embryologically or by trauma with or without some minor epiphysial displacement and subsequently proliferate and lay down bone, giving rise to a tumor.

All investigators of this problem have conceded the possibility of trauma in the etiology of some of the solitary lesions, but it seems unlikely or impossible to explain the multiple and familial types of the disease on this basis alone.

Fig. 4.—*A*, roentgenograms of the right forearm taken immediately after operation and four weeks and twelve weeks later. Note the slipping of the ulnar epiphysis, incomplete reduction, enlargement of the projecting spur of the distal end of the shaft and the distal movement of the epiphysis away from it as growth continued. Also observe the characteristic roentgenographic finding of a giant cell tumor in the distal end of the shaft of the radius in the roentgenogram at the right (twelve weeks after operation). *B*, roentgenograms of the left forearm of the same animal. Similarly persistent partial displacement of the ulnar epiphysis resulted in the formation of cartilaginous exostosis.

Geschickter and Copeland [1] considered cartilaginous exostosis to be

> . . . an exaggeration of a normal bony protuberance intended for the anchoring of an important tendon. At such a junction, nature provides normally for a protuberance of bone bulging through a gap in the periosteum to meet an adjoining tendon, which coöperates in the formation of the attachment by cartilaginous

1. Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, New York, American Journal of Cancer, 1931.

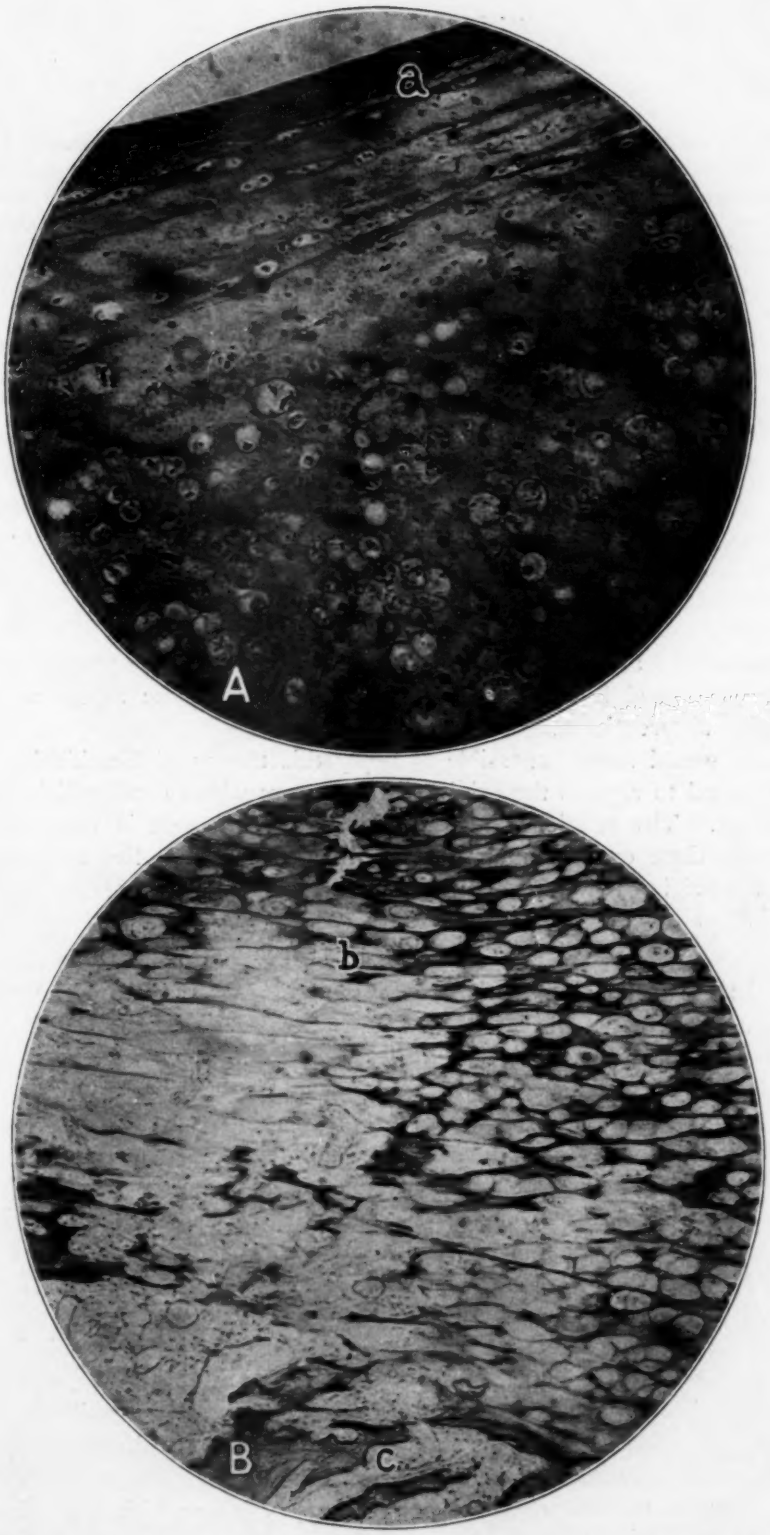

Fig. 5.—High power photomicrographs of cartilaginous exostosis shown in figure 4 *A*. Note the external layer of fibrous tissue covering a layer of cartilage (*a*), the deeper layers of transitional tissue (*b*) varying from calcified cartilage to trabeculae of bone (*c*).

ossification within the substance of the tendon. An exostosis represents a failure in the accurate approximation of the tissue entering into such a junction, the cartilaginous center in the tendon persisting in the form of primitive connective tissue, proliferating in excess, and the protuberance of normal bone beneath extending to form a pedicle or base.

They pointed out:

In both normal tendons, which attach directly to bone and in normal joints at the reflexion of the joint capsule, proliferating zones apparently acting as normal growth centers may be found. In these proliferating centers early cartilage cells derived from young fibroblasts may be seen, and occasional areas of ossification, a transition of tissues typical of osteochondromas.

They expressed the belief that single cartilaginous exostosis may result from traumatism, the injury either repressing the periosteum and preventing it from covering the bone as it would normally or stimulating the growth of cartilage from the precartilaginous tissue in the growth zone in the end of the tendon. They also stated that "osteochondromas are not related histogenetically to the bone proper nor to the epiphyseal line as so often stated," because these tissues are too highly differentiated.

It would seem impossible to apply this theory of Geschickter and Copeland to explain the origin of the tumors which developed in these rabbits. The relationship to epiphysial displacement is too obvious. Again, these experimental findings offer only presumptive evidence as to the origin of this type of tumor in man.

GIANT CELL TUMOR

In the distal fragment of the fractured right radius of one rabbit (fig. 4 *A*) and in the distal end of the diaphysis of the left ulna in another rabbit (fig. 3 *B*) there developed lesions which were roentgenographically, grossly and microscopically indistinguishable from the giant cell tumor of man except for the portion of bone involved (to be discussed later). Also, critical study would no doubt show certain minor differences in cellular morphology. In each instance these soft, friable, vascular reddish brown masses appeared to be definitely circumscribed, to extend to the epiphysial cartilage and to bulge portions of the cortex, which in areas was extremely thin.

The tissue was only loosely attached to the cortex.

The histologic structure illustrated in figure 6 consisted typically of (1) a stroma of spindle and of round cells with large vesicular nuclei loosely disposed around numerous large blood spaces and capillaries and areas of extravasated blood and (2) giant cells containing many small oval nuclei centrally placed and of uniform size.

Thus, in two rabbits there were lesions of bone which were similar to, if not identical with, the giant cell tumor of man. The only variation, the difference in the location of the lesions, is probably more apparent

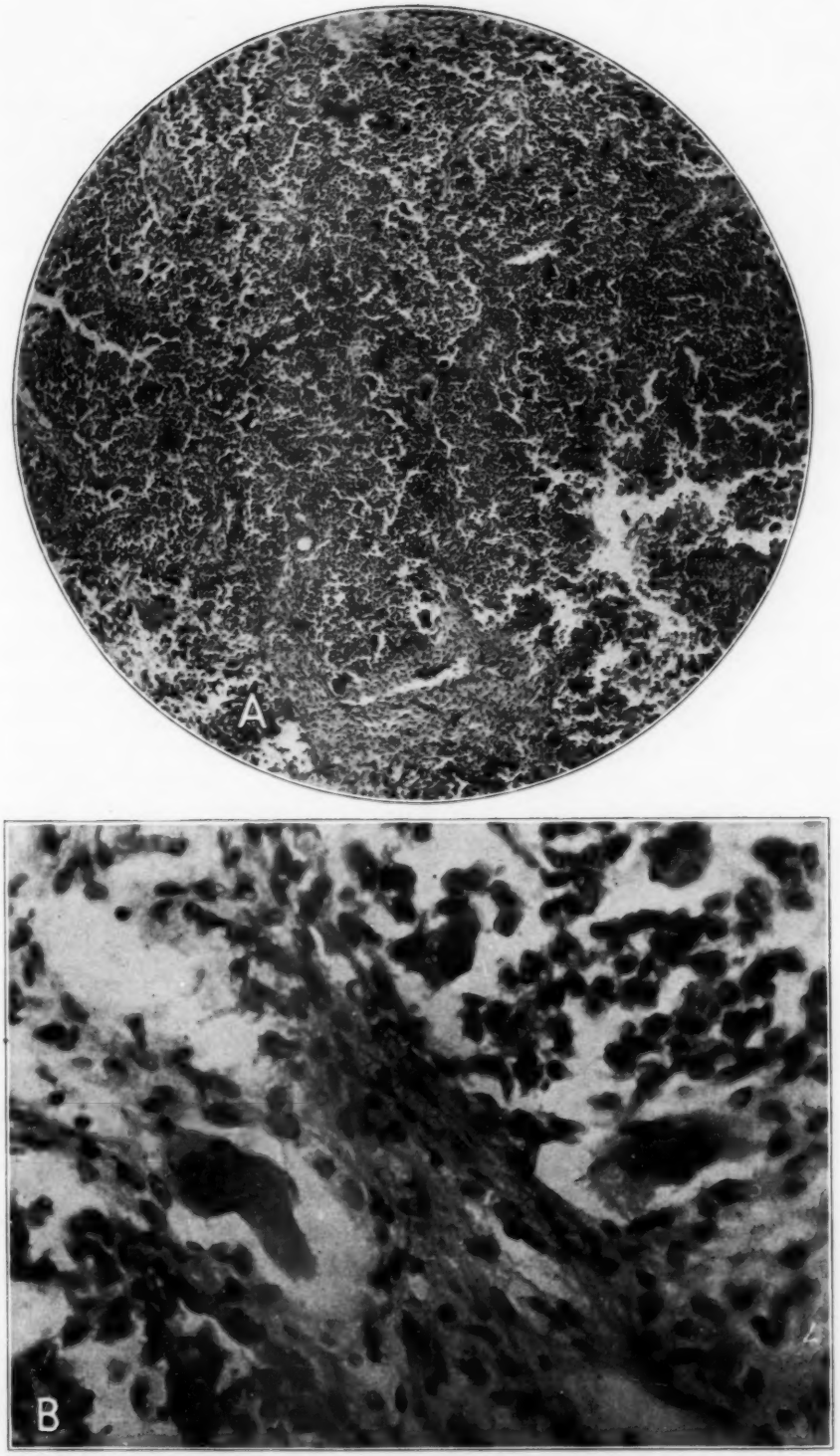

Fig. 6.—*A*, low power photomicrograph of tumor tissue removed from the distal end of the radius of rabbit 3; the tumor is shown roentgenographically in figure 4 *A*. Note the giant cells and stroma typical of a giant cell tumor. *B*, high power photomicrograph of the same tissue.

than real and can be explained on the basis of the immaturity of the animals. Whereas most giant cell tumors in man arise in or involve the epiphysis primarily rather than the metaphysis, as occurred in both rabbits, the tumor in man usually appears after the epiphysial disk has been obliterated. This cartilage was still present in the animals. That the presence of the cartilage similarly alters the location of the tumor in man has been emphasized by Peirce.[2] He stated:

> In the matter of the involvement of the "epiphyses" of the bones, as is common terminology in the older publication particularly, it is of interest that in our series, wherever the epiphyseal discs are still present, the neoplasm has not invaded the disc, being apparently restricted to the end of the diaphysis, the metaphysis, But wherever the epiphyseal disc has been obliterated by the maturity of the bone, the tumor proceeds throughout the cancellous structure to the under surface of the articulating cartilage plate.

Since these tumors did not appear in the roentgenograms taken immediately after operation and first became apparent in those made twelve weeks later, it is obvious that insult to the bone as a result of operation was responsible for their development. In the case of the tumor in the distal end of the radius it is probable that elevation of the periosteum at the time of operation and the subsequent stripping from hemorrhage deprived the distal fragment of much of its blood supply. Also as a result of trauma there was hemorrhage into the medullary portion. Thus there existed, as has been pointed out by Geschickter and Copeland,[1] circumstances conducive to the formation of a giant cell tumor. Their explanation of the process is related in the discussion which follows. In the animal in which the tumor involved the ulna it is probable that the trauma associated with epiphysial separation was the causative factor.

The abnormal association with displaced segments of cartilage in both tumors deserves consideration. It is possible that the transplanted segment of costal cartilage in the radius and the injured displaced segment of epiphysial cartilage in the ulna may have played a part in the formation of the tumors. Ewing [3] and Wright [4] have brought forth evidence of the origin of variants in giant cell tumors from absorption of aberrant islands of cartilage cells which occur not infrequently in children suffering with rickets. They suggested that this process of absorption of cartilage may give rise to neoplastic proliferation.

COMMENT ON GIANT CELL TUMOR

A discussion of the etiology of giant cell tumor involves a consideration of an old controversy into which enters four theories: (1) that the

2. Peirce, C. B.: Giant-Cell Bone Tumor, Am. J. Roentgenol. **28**:167, 1932.

3. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

4. Wright, J., cited by Kolodny.[14]

tumor is a neoplasm or blastoma, (2) that it is an inflammatory lesion on a toxic or infectious basis, (3) that it is of metabolic origin suggested by its occurrence in association with the disturbance in calcium metabolism accompanying hyperparathyroidism and (4) that it represents simply a perverted reparative process in bone in which there has been injury, with resultant hemorrhage and a disturbance of circulation.

The infectious and toxic inflammatory theory has little or no evidence to support it and has been abandoned. Many early observers, among them Nélaton,[5] Paget[6] and Virchow,[7] were impressed with the lack of evidence of anaplasia and with the benign course of the tumor. This fact has constantly been emphasized by the studies of Barrie,[8] Gross,[9] Codman,[10] Bloodgood,[11] Stone and Ewing,[12] Elmslie,[13] Kolodny,[14] Geschickter and Copeland[1] and many others. From a critical review of the literature, Stone and Ewing[12] found not a single authenticated case of malignant degeneration or of dissemination of true metastases of a giant cell tumor.

There is a growing conviction, held by most students of this problem, that a giant cell tumor is merely a "chronic resorptive process" in response to trauma to bone, as suggested by Konjetzny.[15] He arrived at this conclusion from observing the histologic changes which take place in intermedullary hemorrhages, which he was able to show excited a proliferative response in bone marrow productive of the elements found in the giant cell tumor. Similar proof of the traumatic origin of this tumor has been presented by Cone[16] in his investigation of an ossifying hematoma from which he observed that "osteitis fibrosa, hemorrhagic osteomyelitis and giant cell tumor of bone have their representations in

5. Nélaton, E.: Mémoire sur une nouvelle espèce de tumeurs à myéloplaxes, Thèse de Paris, no. 58, 1860.

6. Paget, J.: Lectures on Surgical Pathology, London, Longmans [and others], 1863.

7. Virchows, cited by Stone and Ewing.[12]

8. Barrie, G.: Haemorrhagic Osteomyelitis, Am. J. Surg. **35**:253, 1921.

9. Gross, S. W.: Sarcoma of the Long Bones, Am. J. M. Sc. **78**:17, 1879.

10. Codman, E. A.: Bone Sarcoma, New York, Paul B. Hoeber, Inc., 1925.

11. Bloodgood, J. C.: The Conservative Treatment of Giant-Cell Sarcoma, Ann. Surg. **56**:210, 1912.

12. Stone, W. S., and Ewing, J.: An Unusual Alteration in the Natural History of a Giant Cell Tumor of Bone, Arch. Surg. **7**:280 (Sept.) 1923.

13. Elmslie, R. C.: Fibrocystic Disease of the Bones, in Robert Jones Birthday Volume, London, Oxford University Press, 1928, p. 127.

14. Kolodny, A.: Bone Sarcoma: The Primary Malignant Tumors of the Bone and the Giant Cell Tumor, Chicago, Surgical Publishing Company of Chicago, 1927.

15. Konjetzny, C. E.: Die sogenannte "lokalisierte Osteitis Fibrosa," Arch. f. klin. Chir. **121**:567, 1922.

16. Cone, S.: Ossifying Hematoma, J. Bone & Joint Surg. **10**:474, 1928.

the microscopic pathology of this ossifying hematoma." Geschickter and Copeland [1] reported four cases of subperiosteal giant cell tumor in the shafts of long bones. In these cases, as in most cases of giant cell tumor, there was a history of recent trauma to the site. In the roentgenograms the following picture was observed:

> . . . the periosteum is raised by a tumor casting little or no shadow and resembles a subperiosteal hematoma. At operation, an extremely thin capsule or shell of bone described by most operators as a blue dome presents itself and when incised, a cavity containing blood is found. Tissue removed from this cavity and examined under the microscope shows a structure of typical giant cell areas. . . . In these cases it is clear that trauma and hemorrhage followed by separation of the periosteum are the initial pathologic events.

Geschickter and Copeland expressed the belief that after trauma to the end of a bone there results under certain circumstances a disturbance of the normal processes of repair, "an imbalance between osteoclastic proliferation in the medulla and reactive compact bone in the cortex." They pictured the sequence of events as follows: After trauma there is a hemorrhage which separates the periosteum from the cortex and interrupts its periosteal blood supply, which in turn inhibits the normal reactive processes in the underlying cortical bone. The medullary circulation takes on increased activity in revascularizing the injured area. This takes place only after the osteoclasts have opened up channels in the bone for the budding capillaries. This increased osteoclastic activity is superimposed in an area in which injured and unnourished cortical bone is undergoing necrosis and in which osteoclasts are already unusually active in absorbing bone. "An imbalance is thus created between bone destruction by osteoclasts (and ingrowth of granulation tissue) and new bone formation that would normally proceed from the reactive cortex were its circulation intact."

Ballin and Morse [17] have explained the frequent occurrence of giant cell tumors in association with hyperparathyroidism on the basis of hemorrhage from trauma in osteoporotic bone in which there is already an imbalance. Also, this demineralized type of bone suffers insult with hemorrhage from little or no trauma.

DISTURBANCES IN GROWTH

As stated previously, separation of the distal epiphysis of the ulna took place in twelve of the twenty-eight legs on which operation was performed, and all became completely or nearly completely reduced spontaneously. In seven, the reduction was complete, and in five of these no subsequent disturbance of growth could be detected. In the

17. Ballin, M., and Morse, P. F.: Parathyroidism and Parathyroidectomy, Ann. Surg. **94**:592, 1931.

remaining two and in the five which were incompletely reduced there was, by comparison with the former group, definite evidence of retardation or arrest of longitudinal growth. Since each of these epiphysial separations accompanied a break in the continuity of the companion bone, the radius, deflection deformities anteroposteriorly or laterally from unequal growth from a single epiphysis cannot be determined.

It is fair to conclude, however, that epiphysial separation resulted in a disturbance of longitudinal growth in 58 per cent of instances in the entire group and in 100 per cent of those in which reduction was incomplete.

CONCLUSIONS

1. In growing animals traumatic epiphysial separation in long bones often produces retardation or arrest of longitudinal growth of these bones. These disturbances in growth occurred more often in the animals in which reduction was not complete.

2. The incidental production of cartilaginous exostosis in animals and the relation of this tumor to traumatic separation of the epiphysis and to trauma to the epiphysial cartilage are reported. A suggestion of a comparable etiology in man in certain instances in ventured.

3. The production of a giant cell tumor in two animals incidental to operative trauma to bone is reported. These observations add confirmation to the traumatic and inflammatory theory of the etiology of this type of tumor.

ABSTRACT OF DISCUSSION

DR. L. D. SMITH, Milwaukee: I think that this report is extremely significant and that Dr. Bisgard's interpretation of his data is of great importance.

In this respect it may be that the following phenomena are significant: Recently I removed a four-flanged fixation spike from a healed fracture in the neck of the femur. The spike had been in place for one year. It was much more difficult to remove than to insert. The density of the bone had increased in the immediate neighborhood of the spike with increased cellular tension. I removed at the same time a Steinmann pin which had been in the bone a few days. It was very loose. The flanges of the spike were $6\frac{4}{100}$ inch (1.6 cm.) thick. This thickness did not violate the histologic integrity of the adjacent bone tissue but increased the cellular tension to the point of increasing the pressure on the invading spike. The cylindric pin, because of its geometric properties, required the greatest volume of bone displacement to accommodate it with the least surface friction. Such a pin becomes loose a few hours after its insertion. In one case pressure stimulated the bone cells to greater tonicity, and in the other case it destroyed them.

In some cases of inflammation of bone there is exhibited increased growth; in others, there may be decreased growth. It seems that each phenomenon is a factor not of chemotaxis but of cellular tension, as implied by the chemical and physical phenomena.

The weird growth effects in association with displacement of either end of the radius of the ulna, the other end being intact, are well known. These discrepancies in growth in association with paralysis of the muscles are a familiar manifestation of modified cellular tension.

It is said that irritation is a prolific source of neoplastic growth. It may be that it is a primary phenomenon of cellular tension. It is of interest that Hastings and Eichelberger (The Exchange of Salt and Water Between Muscle and Blood: I. The Effect of an Increase in Total Body Water Produced by the Intravenous Injection of Isotonic Salt Solutions, *J. Biol. Chem.* **117**:73 [Jan.] 1937; cited in The Exchange of Salt and Water Between Muscle and Blood, editorial, *J. A. M. A.* **108**:1893 [May 29] 1937) have observed that an excess of fluid may result in an increase in intracellular fluids without a change in the cell volume.

It has been found in a consideration of the reaction of the erythrocytes in man to dextrose that whereas chemical methods indicate a rapid absorption of dextrose the changes in volume observed by the hematocrit method do not (Luck, J.: Annual Review of Biochemistry, Stanford University Press, Stanford University, Calif., 1935, vol. 4). It is not improbable that physiologic adaptive, compensatory changes in chemical tension are constantly taking place with an attendent change in cellular tension but without a change in the cell volume. This necessarily alters the vibratory frequency of the structure and of the tissue of which it is a part and therefore may be a function of wave phenomena of activated muscle.

It does seem that the phenomenon of cellular tension is an important or essential factor in the growth of tissue. Carey (Studies in the Dynamics of Histogenesis, *Radiology* **13**:1 [July] 1929) has clearly shown the effect of external tension on the growth of bone by the action of muscles. Cellular tension may be either intrinsic or extrinsic and physiologic or uncontrolled. It may be that the interesting observations of Dr. Bisgard demonstrate a phenomenon of disorderly and uncontrolled cellular tension and that the phenomenon of neoplastic growth is related to cellular tension.

CAVERNOUS HEMANGIOMA OF THE SPLEEN

REPORT OF A CASE AND REVIEW OF THE LITERATURE

LEWIS E. SCHOTTENFELD, M.D., C.M.
AND
WILLIAM L. WOLFSON, M.D.
BROOKLYN

Hemangioma of the spleen is rare. This is manifested by the paucity of the literature on the subject and by the fact that Lubarsch reported only three angiomas of the spleen in 19,000 autopsies. The records of the Jewish Hospital yielded data on five cases of cavernous hemangioma of the spleen. The case on which this report is based was one in which a large hemangioma was removed surgically, while in the other four small hemangiomas were discovered at necropsy which had given no symptoms during life. This gives an incidence of 0.14 per cent in 2,800 autopsies.

As a preliminary statement, it might be said that in the past much confusion has existed in the use of the terms angioma and endothelioma and of combinations of these. For the purpose of this paper angioma and endothelioma are employed to denote benignancy.

Hoge [1] in 1895 discussed the pathologic structure of hemangiomas in his report of a case in which operation was performed, with complete recovery. Homans [2] in 1897 cited a case in which 38 quarts (36 liters) of bloody fluid was removed by five paracenteses in one year. At operation the tumor was extirpated without removing the spleen. The symptoms recurred; reoperation resulted in the death of the patient. Huntington [3] aspirated cystic fluid and marsupialized the sac of a splenic tumor which contained blood. The summary of seventy-two cases of splenic cysts reported up to 1912 by Fowler [4] is a classic for completeness and thoroughness. Dowd [5] analyzed a series of fourteen cases reported by others and included the report of a case of his own. Jopson's [6] patient lost 100 pounds (45.4 Kg.), and she complained of a pain and a mass in the left upper quadrant of the abdomen. She made an uneventful

From the Surgical Service and Department of Pathology, Jewish Hospital of Brooklyn.

1. Hoge, M. D.: M. Rec. **48**:418, 1895.
2. Homans, J.: Ann. Surg. **25**:732, 1897.
3. Huntington, T. W.: Tr. Am. S. A. **25**:366, 1907.
4. Fowler, R. H.: Ann. Surg. **57**:658, 1913.
5. Dowd, C. N.: Ann. Surg. **62**:177, 1915.
6. Jopson, J. H.: S. Clin. North America **1**:235, 1921.

ful recovery after splenectomy. Thirty-three angiomas were found in one spleen in a case reported by Müller.[7] Smith and Rusk [8] summarized ninety-seven cases of angiomas and endotheliomas reported in the literature, discussed their possible pathogenesis and classified them under five headings. Moschcowitz,[9] Krumbhaar and Scott [10] and Orlandi [11] contributed to the literature. Wright's case [12] was one of malignant hemangioma of the spleen. Schwarz [13] emphasized the dangers which might follow any procedure other than splenectomy. Zeno and Cid [14] removed a spleen with a lesion reported as hemangio-endothelioma and presented a thorough study of the case. An abscess within a hemangioma of the spleen accounted for the intermittent fever in the case reported by Kellert.[15] Haines and McIlroy's [16] patient, who had an angioma of the spleen, complained of indigestion over a long period, followed by sudden pain, prostration, vomiting and tenderness. Hematoperitoneum and a ruptured spleen were found at operation. The patient died forty-eight hours later.

Other cases have been reported in which no striking features were presented.

PATHOLOGY AND PATHOGENESIS

The cavernous angioma first appears as a circumscribed tumor, developing often on the basis of a congenital nevus, and tends to enlarge steadily over a period of many years. It may be observed at birth or may begin to appear at any age. It may occur anywhere in the body. When allowed to progress, the growth may attain very large dimensions. The course of the tumor is slowly progressive, and it enlarges by distention of the original vessels and by the formation of new vessels. Free anastomosis with large arteries or veins may become established, and severe or fatal hemorrhage may occur. Spontaneous regression may result from contraction of the capsule, thrombosis or inflammation, or a cure may be affected by continuous pressure on the tumor or vessels leading to the tumor.

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7. Müller, H.: Virchows Arch. f. path. Anat. **238**:76, 1922.
8. Smith, C. E., and Rusk, G. Y.: Endothelioma of Spleen: Study of Two Cases, with Review of Literature of Primary Malignancy of Spleen, Arch. Surg. **7**:371 (Sept.) 1923.
9. Moschcowitz, E.: Am. J. M. Sc. **131**:675, 1906.
10. Krumbhaar, E. B., and Scott, J. P.: S. Clin. North America **7**:61, 1927.
11. Orlandi, N.: Virchows Arch. f. path. Anat. **269**:152, 1928.
12. Wright, A. W.: Am. J. Path. **4**:507, 1928.
13. Schwarz, F.: Beitr. z. klin. Chir. **150**:130, 1930.
14. Zeno, A., and Cid, J. M.: Ann. d'anat. path. **7**:583, 1930.
15. Kellert, E.: Am. J. Cancer **16**:412, 1932.
16. Haines, C. E., and McIlroy, P. T.: Spontaneous Rupture of Cavernous Angioma of Spleen, J. A. M. A. **100**:1862 (June 10) 1933.

The pathogenicity of the cavernous angioma is not complex. It consists of a meshwork of fine fibrous connective tissue of different thicknesses which encloses blood filled sinuses of varying sizes and shapes. In the simple hemangioma the connective tissue is noncellular, almost hyalinized. Where these channels are lined by endothelial cells, abnormal and active proliferation of these cells may give rise to a malignant endothelioma.

Hemangioma is a tumor composed of newly formed blood vessels. Opinions as to the origin and growth of such a tumor vary considerably. By means of interstitial injection, Ribbert found that the vessels in the simple hemangioma have few or no lateral anastomoses, from which he concluded that the tumor process is present in an isolated segment of the wall of the vessel and produces elongation and varicosities in a more or less closed territory. The real origin of the hemangioma must be referred to a developmental anomaly in the structure of certain vascular segments which do not fit into the circulatory system and which retain embryonal characters. The congenital origin of the great majority of hemangiomas speaks strongly in favor of a tissue predisposition as a prominent factor in their genesis.

When the vascular channels which comprise the tumor are widely dilated and the connective tissue septums are thin, the angioma is designated as cavernous. Some of these tumors pulsate. Thrombosis and calcific phleboliths may occur in dilated sinuses.

Ewing [17] names these tumors hemangioma simplex and divides them into (1) the common naevus venosus, or telangiectasis of the skin, congenital in origin, (2) the subcutaneous angiomas of children, with local invasion of the underlying structures, and (3) the hyperplastic type of hemangioma hypertrophicum, which grows rapidly and has a poor cellular differentiation. This group he subdivides into (*a*) the capillary type and (*b*) the cavernous type.

When one considers the histologic make-up of the spleen, one finds that from each component of the splenic architecture there can arise a different type of splenomegaly. Fibromas and fibrosarcomas may develop from the capsule and trabeculae; lymphadenomas and lymphosarcomas may originate from the lymphoid elements; angiomas, cavernous angiomas and endotheliomas may be derived from the vascular or sinus endothelium. A cavernous angioma of the so-called benign type may be potentially malignant; the possibility of Ewing's hyperplastic cavernous angioma becoming a malignant endothelioma deserves consideration. Pool and Stillman,[18] in their monograph on "Surgery

17. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

18. Pool, E. H., and Stillman, R. G.: Surgery of the Spleen, New York, D. Appleton and Company, 1923.

of the Spleen," stated that the presence of angiomas in organs other than the spleen does not necessarily indicate that the growths are metastatic from the spleen, since it is well known that angioma may exist as multiple lesions.

After studying the reports of fifteen cases of angioma of the spleen by Smith and Rusk in 1923, only eleven cases with reasonably complete histories have been selected by us for analysis. These, together with the five cases reported after 1923 by others, are as follows:

Smith and Rusk	up to 1923	11 cases
Wright	1928	1 case
Schwarz	1930	1 case
Zeno and Cid	1930	1 case
Kellert	1932	1 case
Authors' case	1933	1 case
		16 cases

The ages of the patients in this series ranged from 1½ years to 56 years. Viewed in decades, the ages are as follows:

Decades	No. of Patients
1-10	1
11-20	3
21-30	2
31-40	3
41-50	2
51-60	4
Not stated	1

Males and females were equally affected. There was one case in this group in which an angioma occurred during pregnancy. In females the occurrence of splenic tumors during the child-bearing period has been noted by Monnier, who explained that during the menses, pregnancy and the menopause there is an engorgement of the spleen. This observation has been corroborated by operations during pregnancy. In three cases in the series there was some form of injury as a possible factor in the development of the tumor. The presence of some toxic or infective agent may predispose the spleen toward the development of angiomas. Chronic malaria predominates in this respect. In two of the sixteen cases here reported there was a history of chronic malaria. The pathogenicity in malaria may offer some explanation for this development. In cases of malaria the spleen is enlarged and soft, and the capsule is thickened and adherent to the surrounding tissues. The pulp is hyperplastic, and the fibrous tissue trabeculae are markedly

thickened. With such a foundation it may be understood how either spontaneously or due to trauma a splenic tumor of the angiomatous type may develop.

SYMPTOMATOLOGY

The symptoms presented by the patient are not all uniform. Only the larger cysts and tumors give rise to symptoms; the small ones often do not manifest themselves clinically. The symptoms may be the result of peritoneal reaction due to a low grade inflammation around the capsule which produces adhesions, causes pain and fever and sometimes induces vomiting. The duration of symptoms varied greatly. In the collected series this ranged from two days to five years. The majority of patients had noted some disturbance from four to eight months before seeking medical aid. In most instances it was a tumor mass alone or with pain which gave the first information that the normal status of the patient had changed.

It is interesting to analyze and study the incidence of the various signs and symptoms which were found in this series of cases of cavernous angioma. In the order of their frequency they are as follows:

	No. of Cases	Percentage
Tumor	16	100.0
Pain	10	62.5
Secondary anemia	2	12.5
Ascites	2	12.5
Loss of weight	3	18.7
Fever	2	12.5
Asthenia	3	18.7
Dyspnea	2	12.5
Jaundice	2	12.5
Leukocytosis	1	6.2
Chills	1	6.2
Constipation	1	6.2
Leukopenia	1	6.2
Pruritus	1	6.2

A mass, confirmed by examination, was by far the outstanding complaint offered by the patient. The sizes of the tumors varied. They were situated in the left side of the hypochondrium, the epigastrium or the middle of the abdomen or projected toward the left lumbar region. A tumor may be fixed or movable, smooth or irregular, firm or elastic, depending on the density of the adhesions to the surrounding organs, whether the tumor is solid, cystic or multilocular, on the amount of retraction due to fibrous connective tissue and on the tension of any cystic contents of the tumor.

Pain manifested itself in various ways. It was sharp or pressure-like or gave a sensation of heaviness or dragging. It was usually present in the left upper quadrant of the abdomen and in the epigastrium. Symptoms of pressure produced by the large splenic tumors were evidenced by digestive disturbances, such as constipation or diarrhea. A definite complaint of pain occurred with most large splenic tumors. It was present in 62.5 per cent of the group. Monnier mentioned a friction rub heard in some cases, which was due to perisplenitis.

Weakness and loss of weight were named as complaints in 18.7 per cent of the cases.

In 12.5 per cent of the group the following symptoms were found: anemia, ascites, dyspnea, fever and jaundice. Secondary anemia was possibly due to some direct effect of the angioma on the hematopoietic system, of which the spleen forms an integral part. This in some way may have influenced the hemolysis of the red blood cells or inhibited hyperplasia of the bone marrow. Ascites may become excessive and cause discomfort. Abdominal paracentesis was repeatedly performed in Homan's case for this reason. Necrosis or thrombosis within the spleen or splenic tumor or in the splenic veins may be the cause of the elevation in temperature. Secondary infection was also recorded and resulted in one case in the formation of an abscess. Dyspnea occurred when a large cavernous angioma of the spleen impinged on the diaphragm, compressed the lungs and reduced the respiratory effort and the vital capacity. The pathogenesis of jaundice, although not stated, can easily be comprehended because of the high incidence of metastasis to the liver with biliary obstruction.

More infrequently, in 6.2 per cent of the cases, there was leukocytosis, leukopenia, chills, pruritus or constipation. The occurrence of chills with or without a cellular response in the blood was in all probability due to the invasion of the blood stream with small emboli, either bacterial or necrotic material from the tumor, which so closely borders on the blood vessels of the spleen.

METASTASIS

The liver was the seat of angioma in six cases of the series. The lesion was also found in single instances in the lymph nodes, pancreas, stomach and intestines, lungs and pleura and in the vertebrae. Whether these lesions were true metastases or occurred concomitantly with the angiomas of the spleen was not definitely cited. In the liver the lesion was probably an extension from the splenic vein through the portal system. When the stomach and intestines were involved, the spread probably occurred by contiguity, because dense adhesions intervened

between the splenic tumor and the stomach. The sites of metastases were as follows:

	No. of Cases	Percentage
Lymph nodes	1	6.2
Liver	6	37.5
Pancreas	1	6.2
Stomach and intestine	1	6.2
Lungs and pleura	1	6.2
Vertebrae	1	6.2

DIAGNOSIS

Before operation the diagnosis of a primary hemangioma of the spleen is difficult. An angioma may be considered when there is a history of a previous malarial infection, trauma or pregnancy followed at some variable time by a tumor in the left side of the hypochondrium or the epigastrium. A diagnosis may be more suggestive when there is pain, loss of weight, asthenia, secondary anemia, ascites or fever associated with the tumor. The presence of a metastasis to the liver, when large enough to be palpated, may be helpful.

It is necessary to differentiate by clinical and roentgenographic investigation a large lesion of some other organ from a splenic tumor. A cyst of the omentum, mesentery, pancreas or left lobe of the liver, although rare, must be considered. An enlarged kidney, due to any of various causes, cystic, inflammatory or neoplastic, may be displaced from the lumbar fossa posteriorly to occupy a more anterior position. A neoplasm of the splenic region of the colon is occasionally of such size that it must be distinguished from one of the splenic organ. A pedunculated ovarian cyst that ascends from the pelvic region toward the left lumbar and upper abdominal quadrant must be thought of. A retroperitoneal tumor may attain enormous dimensions and cause some confusion in diagnosis.

TREATMENT

In Fowler's summary of the treatment in seventy-two cases reported up to 1912 it was found that surgeons up to that time had treated cavernous hemangioma of the spleen (1) by puncture, (2) by incision and drainage of the tumor mass with marsupialization of the tumor sac, (3) by excision of the tumor and (4) by splenectomy. Splenectomy was the operation of choice in twenty-five (34.7 per cent) of the seventy-two cases and yielded the best results.

Operation was performed in fourteen of the sixteen cases which form the basis of this study. In twelve the entire spleen was removed, in one a partial splenectomy was done and in another the spleen was left in situ after an exploratory operation on the abdominal cavity.

The remaining two cases of the series were fatal, and at necropsy a hemangioma was found. In one of these, angiomas were found in other organs. Of thirteen cases in which the spleen was either totally or partially removed, cure was obtained in ten. Death occurred in two cases shortly after the operation and in one four weeks later. In the remaining case, in which an exploratory operation was done, death occurred sixty hours later. Thus, 62 per cent of the patients in this series who were subjected to splenectomy were cured. The operative mortality was 21.4 per cent; included in this estimate of mortality are the two cases in which death occurred immediately after the operation and the one in which death occurred sixty hours later. The case in which death

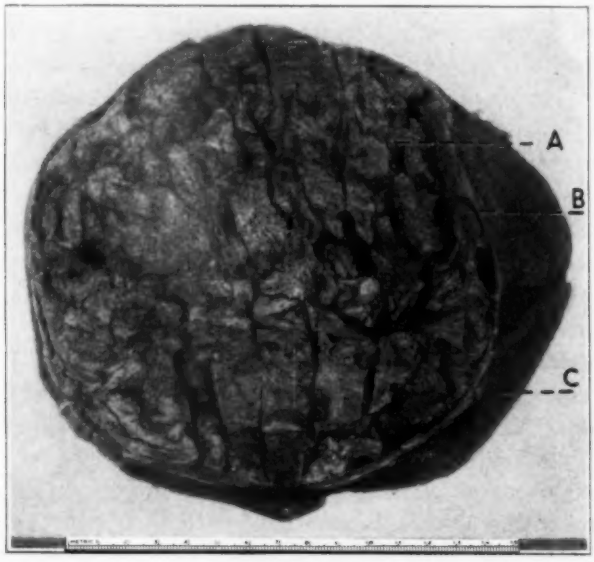

Fig. 1.—Gross specimen of a hemangioma of the spleen. *A* indicates the hemangioma, *B*, the capsule of the tumor, and *C*, splenic tissue.

occurred four weeks later cannot be considered one of "operative death." Early splenectomy is urged in cases of cavernous hemangioma of the spleen. Otherwise certain dangers may be anticipated, such as spontaneous rupture, fatal hemorrhage or malignant transformation, as pointed out by Schwarz.[18]

REPORT OF CASE

History.—D. B., a white woman aged 31, was admitted to the Jewish Hospital on Dec. 21, 1933, to the service of Dr. William L. Wolfson. She complained of a large swelling in the left upper quadrant of the abdomen, which had been present for seven years. The mass had grown steadily larger. Ten weeks prior to admission she had twinges of pain over the region of the tumor. There had been no loss of weight, strength or appetite during the past seven years. No

abnormal digestive or urinary symptoms were presented. No prolonged bleeding was noted during the menstrual periods or after any minor injuries.

The family history and the past history were irrelevant.

Physical Examination.—The patient appeared well nourished, of good color and not acutely ill. Both pupils were equal and reacted to light and in accommodation. The heart and lungs were normal. The left upper quadrant of the abdomen was noticeably prominent. A tumor, firm, smooth and tender, occupied the entire left side of the hypochondrium and the left lumbar region. The liver and kidneys were not enlarged.

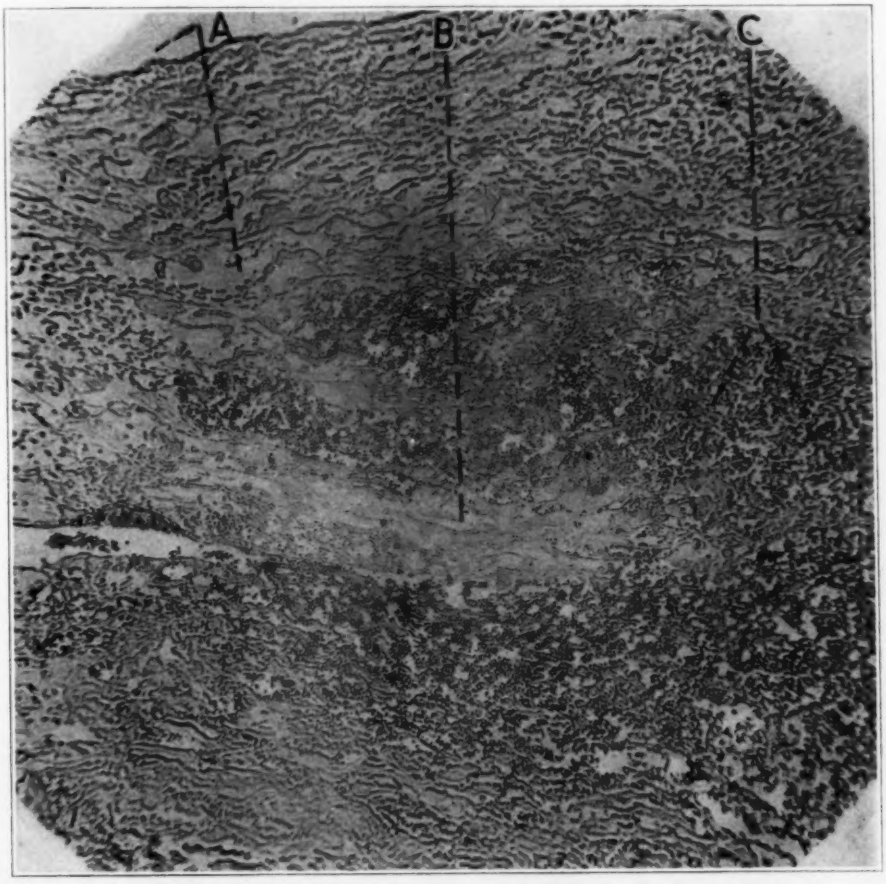

Fig. 2.—Low power photomicrograph of the hemangioma of the spleen. *A* indicates blood filled sinuses; *B*, hyalinizing connective tissue stroma, and *C*, red blood cells.

The temperature was 99.4 F., the pulse rate 90 per minute and the respiratory rate 20 per minute. The systolic blood pressure was 124 mm. of mercury and the diastolic pressure 90 mm. Urinalysis gave negatiye results. The red blood cell count was 3,400,000, and the hemoglobin content 63 per cent (Dare). The leukocyte count was 7,800 with 65 per cent polymorphonuclear cells (band

forms, 5 per cent), 4 per cent eosinophils, 2 per cent basophils, 27 per cent lymphocytes, and 2 per cent monocytes. There were slight anisocytosis and poikilocytosis. Some oligochromasia was present. The fragility test showed that hemolysis began with a concentration of sodium chloride of 0.42 per cent and was complete with 0.30 per cent. Chemical analysis of the blood showed: sugar, 154 mg. per hundred cubic centimeters of blood; creatinine, 1.2 mg.; urea nitrogen, 11.2 mg., and uric acid, 5 mg. The carbon dioxide-combining power was 49.7 volumes per hundred cubic centimeters of blood.

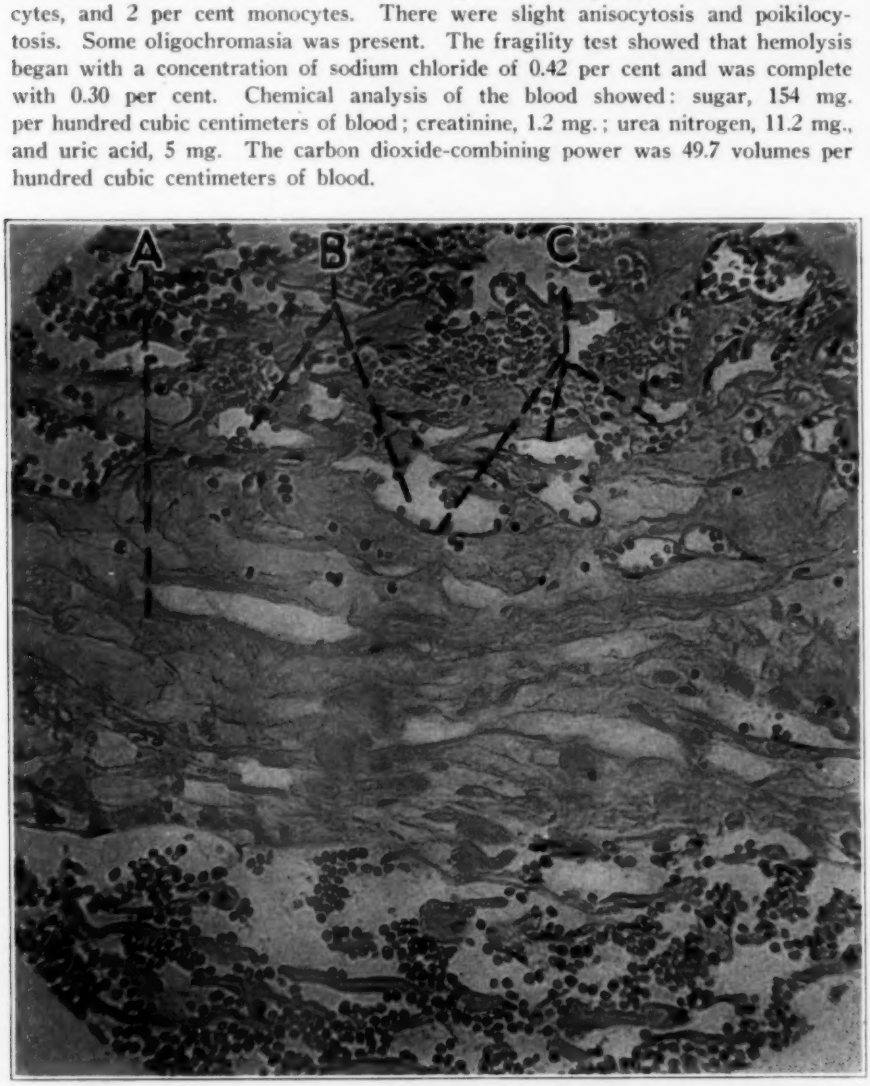

Fig. 3.—High power photomicrograph of the hemangioma of the spleen. *A* indicates hyalinizing connective tissue stroma; *B*, blood sinuses, and *C*, endothelial cells lining the sinuses.

A study of the pneumoperitoneum disclosed a large tumor in the left side of the hypochondrium, the borders of which were smooth and not adherent. Inferiorly it was limited by the lienorenal ligament. The mass was about the size of a Cassawba melon and was splenic in origin.

The patient was given a transfusion of blood the day before the operation.

Operation.—Through an upper left rectus incision into the abdominal cavity there was disclosed a large red-brown spleen, which was smooth on the surface.

A major part of it extended from beneath the left costal margin toward the middle of the abdomen. On the outer surface there was a large plaquelike area the size of a small saucer, distinctly discolored, yellowish white and slightly raised above the general surface. Beneath this area the splenic pulp was mushy and almost cystic. The spleen was singularly clear of adhesions and was readily dislocated forward and upward. The liver, ovaries and kidneys were normal. A splenectomy was easily performed. The abdominal wound was closed without drainage.

The patient was discharged thirteen days after operation. When last seen, on May 22, 1935, she was perfectly well. The abdominal wound was entirely healed.

Pathologic Report (Dr. Max Lederer).—The spleen measured 21 by 18 by 10 cm. (fig. 1). The major part was whitish, and the rest was the color of a normal spleen. The entire surface was somewhat dull. The consistency was semisolid. On section, it was composed of a small rim of compressed splenic tissue, whereas the remainder was occupied by an encapsulated circumscribed mass of yellowish and brown tissue. This mass measured 16.5 cm. in diameter. The consistency of the mass in some parts was rather firm and in other parts gelatinous. On sectioning the yellow masses of tissue, numerous spaces were disclosed with clear and pink fluid. The capsule was composed of a thick hyalinized mass, which was rough and contained areas of calcific deposits.

Microscopic Examination (fig. 2).—The encapsulated mass showed almost entirely necrotic and degenerated tissue. In many places there was a network of trabeculae forming irregularly sized and shaped spaces, which contained both fresh and old blood. These trabeculae in some places were very delicate; in others they consisted of broad bands of connective tissue. The nuclear elements had completely disappeared. Thrombi were seen in the larger spaces. The capsule was made up of a lamellated mass of hyaline tissue containing numerous spaces and deposits of calcium (fig. 3). The remaining splenic tissue, except for areas of compression, was normal. The diagnosis was hemangioma of the spleen with degenerative changes.

SUMMARY

A case of cavernous hemangioma of the spleen with successful treatment by splenectomy is recorded.

A review of the literature on cavernous hemangiomas of the spleen is briefly outlined, with an analysis and discussion of the clinical and pathologic aspects.

EXPERIMENTAL SUBTOTAL LIGATION OF THE ARTERIES SUPPLYING THE LIVER

CHARLES HUGGINS, M.D.
AND
JOSEPH POST, M.D.
CHICAGO

It was found that subtotal removal of the arterial supply of the liver in the dog was possible by means of multiple stage operations, a procedure which was fatal when carried out at one sitting.

The liver, lungs and placenta may be set apart from the other organs of the body since they receive blood of two different compositions, based on the oxygen and the carbon dioxide content. The relative contributions of the hepatic artery and the portal vein to the circulation of the liver, as well as the total flow of blood through the liver, have been estimated. The total amount of blood flowing through the liver per gram of liver per minute has been found by various investigators to be from 0.43 to 0.7 cc.,[1] from 0.46 to 1.12 cc.,[2] 0.25 cc.,[3] 0.84 cc.,[4] from 0.63 to 1.44 cc.,[5] and 0.75 cc.[6] The percentage of the circulation of the liver contributed by the hepatic artery has been found to be from 12 to 25 per cent,[1] from 20 to 25 per cent,[7] from 12.6 to 24.5 per cent,[2] 30 per cent,[4] and from 26 to 32 per cent.[5]

The question arose whether the liver could survive on blood from the portal vein when deprived of the major amount of its arterial blood supply.

REVIEW OF THE LITERATURE

An extensive literature exists on ligation of the hepatic arteries.[8] Haberer established three criteria which have removed many of the pitfalls in the investigation of this subject present in the older reports. They are as follows: (1) The point of ligation should be accurately stated, (2) the experiment should be terminated with arterial injection

From the Department of Surgery of the University of Chicago.

1. Grab, W.; Janssen, S., and Rein, H.: Ztschr. f. Biol. **89**:324, 1929.
2. Blalock, A., and Mason, M. F.: Am. J. Physiol. **117**:328, 1936.
3. Schmid, J.: Arch. f. d. ges. Physiol. **125**:527, 1908.
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6. Barcroft, J., and Shore, L. E.: J. Physiol. **45**:296, 1912.
7. Schwiegk, H.: Arch. f. exper. Path. u. Pharmakol. **168**:693, 1932.
8. (*a*) Haberer, H.: Arch. f. klin. Chir. **78**:557, 1905. (*b*) Narath, A.: Deutsche Ztschr. f. Chir. **135**:305, 1916. (*c*) Cameron, G. R., and Mayes, B. T.: J. Path. & Bact. **33**:799, 1930.

to establish collateral circulation and (3) the operation should be done with asepsis. The anatomic relationships of the hepatic artery in the dog, the cat and man are essentially similar, and the experimental findings reported in the literature may be summarized as follows on the basis of the point of ligation:

1. Acute ligation of the hepatic artery proximal to its junction with the gastroduodenal artery (fig. 1, *1*). The operation on dogs was compatible with life; no changes were found in the liver.[9] The results obtained on rabbits were similar to those obtained on dogs.[10]

2. Acute ligation of the hepatic artery proximal to its junction with the right gastric artery (fig. 1, *2*). No changes were observed in dogs.[11]

3. Acute ligation of the hepatic artery distal to the entrance of the right gastric artery (fig. 1, *3*). Haberer [8a] found that all animals except a few with large phrenic arteries died in from one to three days after operation with hepatic necrosis; in those that survived the liver was normal. Other observers found that death always occurred within a few days,[12] and others, that the operation was always fatal, with terminal hypoglycemia [13] which was not relieved by the administration of epinephrine and was caused by complete absence of glycogen in the liver, heart and skeletal muscles.[14] Some workers found the operation compatible with life and have seen no appreciable changes in the liver.[15] (In the experiments of Janson the point of ligation was not accurately described.) Many observers found that in the rabbit, provided there was no accessory artery, necrosis, liver infarcts and death usually occurred within six days.[16]

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9. (*a*) Putzu, F.: Arch. ital. di chir. **37**:483, 1934. (*b*) Livierato, S.; Vagliano, M., and Dervenaga, A.: Ann. d'anat. path. **12**:787, 1935. (*c*) Behrend, M.; Radasch, H. E., and Kershner, A. G.: Comparative Results of Ligation of Hepatic Artery in Animals: Its Application to Man, Arch. Surg. **4**:661 (May) 1922. (*d*) Haberer.[8a]

10. Cameron and Mayes.[8c] Putzu.[9a] Behrend, Radasch and Kerschner.[9c]

11. (*a*) Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**: 278, 1909. (*b*) Haberer.[8a] (*c*) Putzu.[9a]

12. Narath.[8b] Livierato, Vagliano and Dervenaga.[9b]

13. Collens, W. S.; Shelling, D. H., and Byron, C. S.: Am. J. Physiol. **78**: 349, 1926.

14. Collens, W. S.; Shelling, D. H., and Byron, C. S.: Am. J. Physiol. **79**: 689, 1927.

15. (*a*) Janson, C.: Beitr. z. path. Anat. u. z. allg. Path. **17**:505, 1895. (*b*) Whipple and Sperry.[11a]

16. Loeffler, L.: Factors Determining Necrosis or Survival of Liver Tissue After Ligation of Hepatic Artery, Arch. Path. **21**:496 (April) 1936. Steckelmacher, S.: Beitr. z. path. Anat. u. z. allg. Path. **57**:314, 1913. Cohnheim, J., and Litten, M.: Virchows Arch. f. path. Anat. **67**:153, 1876. Cameron and Mayes.[8c] Putzu.[9a] Janson.[15a] Behrend, Radasch and Kershner.[9c]

4. Acute ligation of a branch of the hepatic artery to the liver (fig. 1, *4*). Haberer [8a] found the operation usually well borne by the dog; two animals died of peritonitis. Putzu [9a] found minimal hepatic changes compatible with life. Necrosis always occurred in the rabbits.[17]

The chief difference between the dog and the rabbit occurs in ligation of the branches of the hepatic artery, owing to a difference in the collateral circulation. The site of acute ligation is important in determining the course.

5. Ligation of the hepatic artery in stages. Haberer ligated the common hepatic and gastroduodenal arteries in one dog and one cat

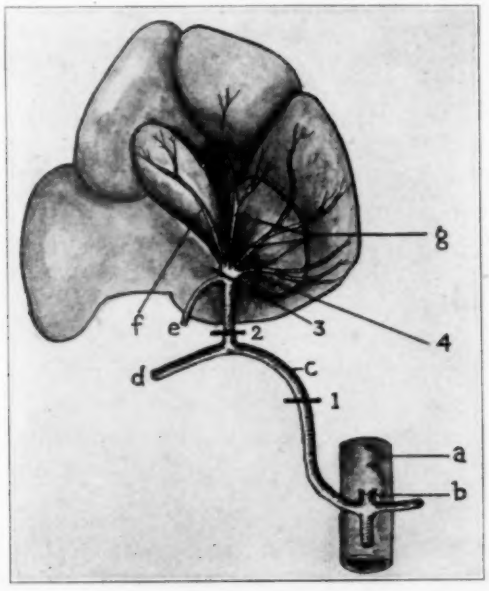

Fig. 1.—Diagram of the arterial supply to the liver of the dog: *a*, the aorta; *b*, the celiac axis; *c*, the common hepatic artery; *d*, the gastroduodenal artery; *e*, the right gastric artery; *f*, the cystic artery; *g*, the branches of the hepatic artery to the liver.

(fig. 1, *1* and *2*); one month later the branches to the liver distal to the preliminary ligation were ligated (*3*). The dog survived these operations, but the cat died in ten hours. Livierato and his colleagues [9b] ligated the hepatic artery in dogs (fig. 1, *1*) and subsequently removed this structure at the porta, as was done in our experiments. Their dogs survived from four to six days after the last operation and appeared normal.

17. Haberer.[8a] Cameron and Mayes.[8c] Putzu.[9a]

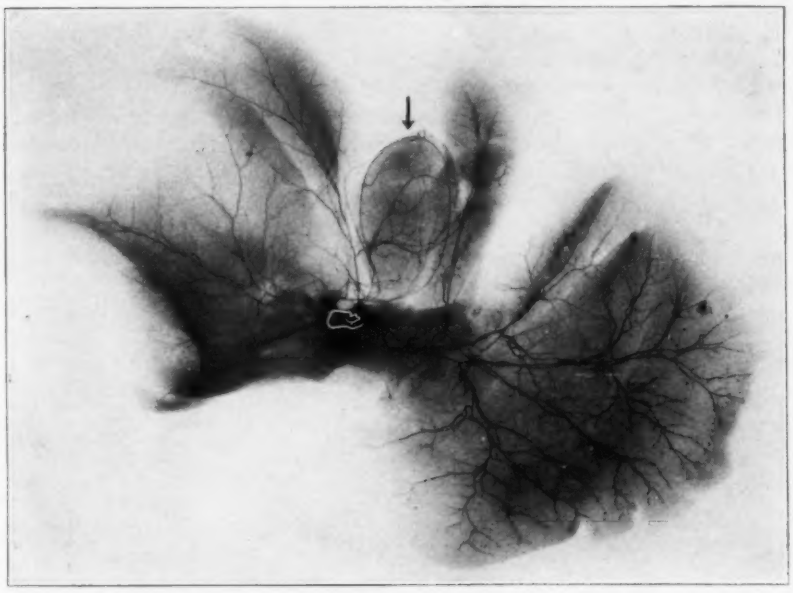

Fig. 2.—The arterial system of the liver of a normal dog. Barium sulfate-acacia solution was injected at a pressure of 200 mm. of mercury through the thoracic aorta. A fine wire encircles the gallbladder (see arrow).

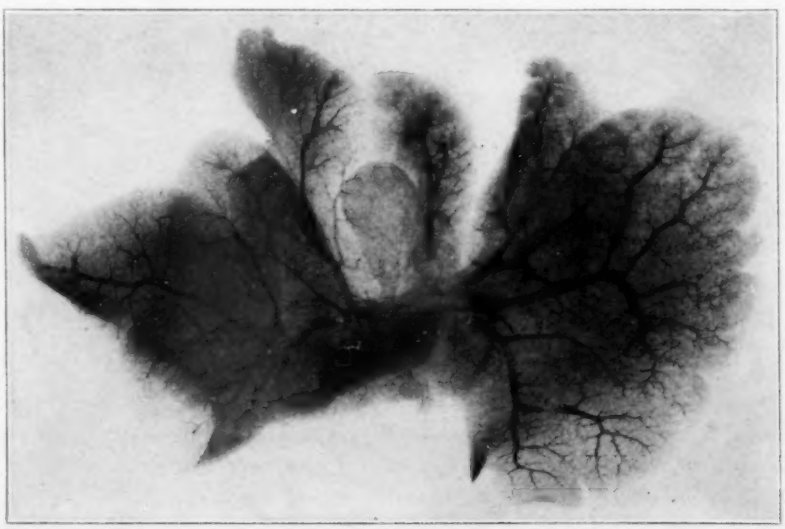

Fig. 3.—The portal system of a normal dog. Barium-acacia solution was injected through the portal vein.

EXPERIMENTAL DATA

All operations were done with the animals under ether anesthesia with asepsis.

EXPERIMENT 1.—*Acute ligation of the hepatic artery and its principal collaterals, the right gastric and gastroduodenal arteries* (fig. 1, *3*).

The arteries just mentioned were doubly ligated and sectioned between the ligatures in nine dogs. In each case a fatal result occurred: Seven dogs with the typical symptoms of liver autolysis died within seventy-two hours, and the others, at seven and twelve days (table 1). Peritonitis was present in each animal,

TABLE 1.—*Results of One Stage Ligation of the Hepatic, Gastro-Duodenal and Right Gastric Arteries in Dogs*

Dog No.	Operation	Survival Time	Course	Pathologic Picture
1	Ligation of hepatic, gastroduodenal and right gastric arteries	<24 hr.	Great postoperative thirst and vomiting; pulse rate 140; temp. 40 C. (104 F.)	Bloody fluid in peritoneal and pleural cavities; severe central hemorrhage but no inflammatory reaction in liver
2	Same as on dog 1	<24 hr.	.....	No free fluid in peritoneal cavity; liver swollen and red
3	Same as on dog 1	20 hr.	Great thirst and vomiting; temp. 39.2 C. (102.2 F.)	No free fluid; liver friable and swollen; mottled areas of infarction
4	Same as on dog 1	33 hr.	Moderate vomiting; temp. 37-38.2 C. (98.6-100.8 F.); slight glycosuria; terminal convulsions (blood dextrose 39.6 mg. per 100 cc.) and blood concentration	Bloody fluid in peritoneal and pleural cavities; liver swollen and very red; mostly normal on histologic examination except for central hemorrhage and areas of coagulation necrosis
5	Same as on dog 1	7 days	Bradycardia (pulse rate 68-80) for 24 hr.; dog seemed normal for 6 days	Bloody fluid in peritoneal and pleural cavities; liver very red and friable
6	Same as on dog 1	12 days	No fever for 2 days; blood dextrose normal (86 mg. per 100 cc.); died of perforation of gallbladder	Bloody fluid in peritoneal and pleural cavities; liver grossly and microscopically normal
7	Ligation of hepatic and gastroduodenal arteries	24 hr.	.....	Bloody fluid in peritoneal cavity; liver very swollen and red with patches of necrosis
8	Same as on dog 7	40 hr.	In good condition for 30 hr.	Sponge liver; extensive necrosis
9	Same as on dog 1 plus ligation of common bile duct	<72 hr.	Temp. 36.5-38 C. (97.9-100.4 F.); much thirst and vomiting; bile and albumin ++++ in urine; blood dextrose 51.3 mg. per 100 cc.	Purulent peritoneal fluid; liver very red with necrotic areas

and usually there was bloody fluid in the peritoneal and pleural cavities, as described by Haberer,[8a] in association with hepatic necrosis.

EXPERIMENT 2.—*Subtotal removal of the arterial supply to the liver. Preliminary ligation of the hepatic artery proximal to its communication with the gastroduodenal artery. Subsequent excision of the hepatic arteries at the porta hepatis and subsequent ligation of the phrenic arteries.*

In the earlier experiments the hepatic artery was gradually compressed with a metal clamp devised by Goldblatt and his co-workers,[18] but for these purposes

18. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: J. Exper. Med. **59**:347, 1934.

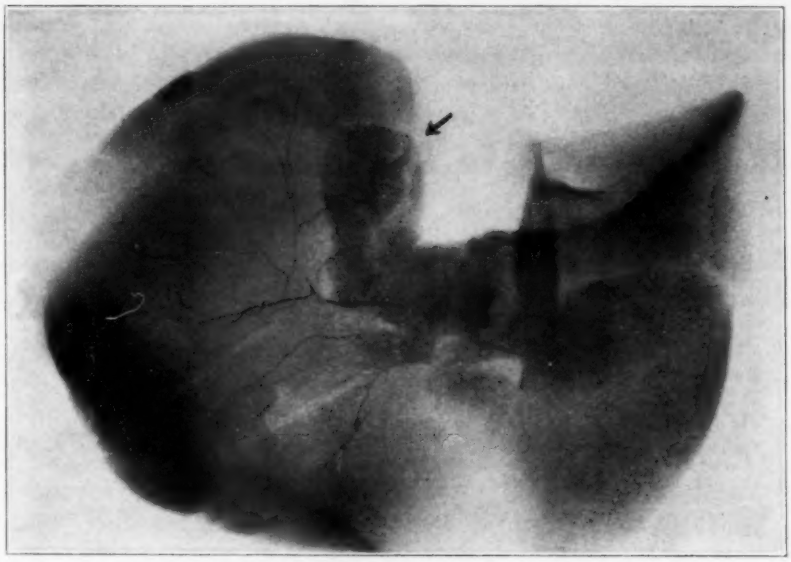

Fig. 4.—The arterial system of the liver of a dog after removal of the hepatic artery and ligation of the right gastric, gastroduodenal, cystic and left phrenic arteries (table 2, dog 7). Barium-acacia solution was injected through the aorta. The right phrenic supply may be seen. The arrow points to the gallbladder.

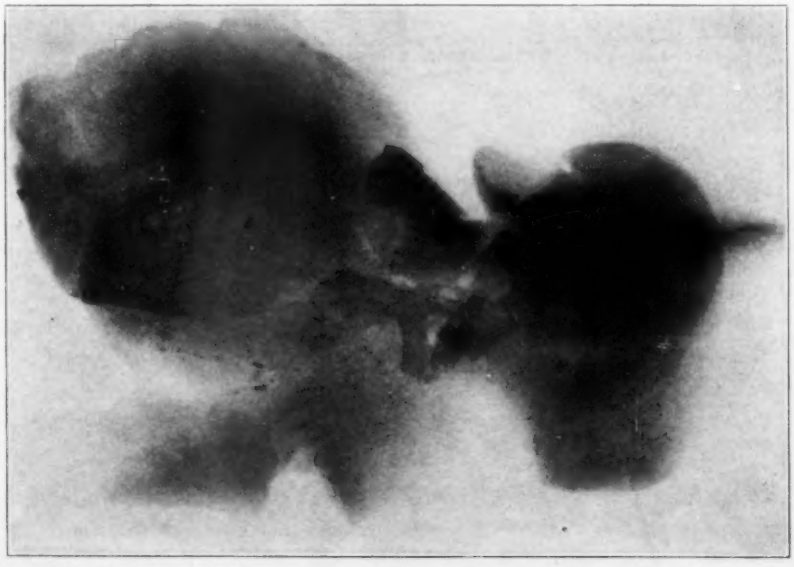

Fig. 5.—The arterial system of the liver of a dog after subtotal arterial removal (table 2, dog 5). Barium-acacia solution was injected through the aorta at a pressure of 200 mm. of mercury.

a double ligature of the hepatic artery (fig. 1, *1*) with section was more efficient and was used exclusively in later experiments. From one to four weeks later the gastroduodenal and right gastric arteries were doubly ligated, and the hepatic artery was dissected and excised and its branches ligated where they entered the liver; about 2 cm. of the cystic artery was removed with the entire hepatic artery and 2 cm. of each of the individual branches to the liver.

TABLE 2.—*Results of Multiple Stage Ligation of Hepatic Artery and Its Principal Collaterals in Adult Dogs*

Dog No.	Operation	Course	Pathologic Picture	Comment
1	Hepatic artery two-thirds occluded at 0 days; completely occluded* after 22 days; ligation of right gastric and gastroduodenal arteries after 33 days	Gained weight; active; appeared normal; killed after 92 days	Gallbladder shrunken, increased fibrosis; fatty infiltration of liver (++); area of round cell infiltration (+)	Hepatic artery not excised
2	Right gastric and gastroduodenal arteries excised at 0 days; hepatic artery three-fourths occluded* after 11 days and ligated after 33 days	Appeared normal; killed after 62 days	No changes in liver or gallbladder	Hepatic artery not excised
3	Right gastric and gastroduodenal arteries ligated and hepatic artery one-half occluded* after 0 days; completely occluded after 15 days; arteries at porta excised after 29 days	Appeared healthy; killed after 45 days	Slight round cell infiltration of liver; normal distribution of carbon in Kupffer cells	
4	Right gastric and gastroduodenal arteries with partial occlusion of hepatic artery at 0 days; hepatic artery completely occluded after 9 days	Seemed normal; killed after 21 days	Postmortem injection of aorta with barium showed blood entering liver through phrenic arteries; slight round cell infiltration	Injection with 12.5% india ink (30 cc.) at 41 and 43 days intravenously
5	Hepatic artery ligated at 0 days; arteries at porta excised after 13 days; phrenic arteries ligated after 22 days	Appeared healthy; killed after 35 days	Hepatic cells foamy with high grade vacuolization; gallbladder much shrunken; acute cholecystitis; much submucosal infiltration of polymorphonuclears and connective tissue proliferation in the wall	Circulation time, 75 sec.
6	Hepatic artery ligated at 0 days; arteries at porta excised after 7 days	Apparently normal; killed after 29 days	Gallbladder normal; liver cells very foamy	Circulation time, 85 sec.
7	Same as on dog 6; left diaphragm vessels ligated after 17 days	Normal behavior; killed after 29 days	Much cholecystitis with polymorphonuclear and connective tissue proliferation	Circulation time, 90 sec.
8	Gastroduodenal and right gastric arteries ligated at 0 days; dummy abdominal operations after 11, 21 and 30 days	Normal behavior	Liver cells very foamy	Control experiment

* Occlusion with the clamp described by Goldblatt, Lynch, Hanzal and Summerville.

In three dogs at a further sitting the peritoneal attachments of the liver to the diaphragm, esophagus, stomach and posterior abdominal wall were removed, and the adventitia was removed from the hepatic veins with sharp dissection. In two of the latter three dogs, both phrenic arteries were also ligated, while in the third the left phrenic artery only was ligated. This operation was tedious and was best carried out through a long midline anterior incision.

The results are shown in table 2. There was no fatality in this series. The dogs were in good condition after operation, gained weight and were killed after from twelve to ninety-two days. The chief abnormality noted at necropsy was a shrunken gallbladder, the site of an acute cholecystitis with inflammatory changes extending throughout the wall. The liver showed no abnormalities. In some cases the cells were slightly fatty, in others there was slight cellular infiltration, and in yet others foamy cells, but we have frequently seen these changes in dogs supposed to be normal.

The arterial circulation time was determined. After surgical exposure the portal vein was ligated, and 10 cc. of 15 per cent solution of sodium ferrocyanide ($Na_4Fe(CN)_6.12\ H_2O$) was rapidly injected into an exposed femoral vein, the beginning of the injection being noted with a stop watch. An incision was then made in the liver, and the blood oozing from the cut surface was collected on gauze saturated with 10 per cent solution of nitric acid and 10 per cent solution of ferric chloride. The time of first appearance of the prussian blue color was noted. In three normal dogs the time of appearance was twenty, twenty-one and twenty-eight seconds. In three dogs with subtotal arterial removal the time of appearance was seventy-five, eighty-five and ninety seconds. In two dogs with subtotal arterial removal the oxygen content (in volumes per cent) of the portal vein was 16.10 and 10.88, and that of the hepatic vein, 12.89 and 4.82, respectively.

EXPERIMENT 3.—*Acute ligation of the common hepatic artery in rats.*

This structure was ligated just after its origin from the celiac axis in seventeen albino rats. Eleven died within seventy-two hours (65 per cent); five died before the twelfth day, and one died on the twenty-eighth day. The liver of the rats which died on or before the twelfth day usually showed large areas of coagulation necrosis and infarction; the necrotic areas frequently involved more than half a lobe. It was frequently found that areas of the liver appeared normal while others were extensively necrotic.

COMMENT

Within recent years three opinions have been given regarding the necessity of arterial blood for survival of the liver. Cameron and Mayes (1930) stated that "the liver cells die when they are deprived of arterial blood." According to Loeffler (1936), "it can be concluded without objection from the results of my experiments on rats and rabbits that the liver can survive on portal vein blood alone." Livierato, Vagliano and Dervenaga, who removed the hepatic artery in stages (1935), stated that "the complete privation of arterial blood does not influence the life of the animal."

In the present experiments it was found that acute ligation of the principal vessels at the porta hepatis was always fatal. The outcome seemed to be directly related to liver autolysis, the lethal effects of which have been explained satisfactorily by Ellis and Dragstedt [19] and by Andrews and Hrdina [20] as due to infection by anaerobic bacteria of the Clostridium Welchii group normally present in the livers of grown

19. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

20. Andrews, E., and Hrdina, L.: Surg., Gynec. & Obst. **52**:61, 1931.

dogs. A consideration of a single animal (table 1, no. 6) which died twelve days after operation from a ruptured gallbladder leads one to suppose that this operation may not be invariably fatal as would appear from the experiments of Haberer and of Whipple and Sperry.

In contrast with sudden ligation of the principal arterial supply are the experiments in which ligation in multiple stages was done, which was well borne by the animals. The greatest changes developed in the gallbladder, in which acute cholecystitis occurred frequently. Apparently if the arterial circulation is gradually reduced, death from anaerobic bacteria does not occur and the liver becomes accommodated to deprivation of most of its arterial blood.

It seems impossible to remove arterial blood completely from the liver. In addition to the hepatic and phrenic arteries and fine vessels in the lesser omentum and from the esophagus which may be removed in stages, there are fine arterioles (vasa vasorum) in the hepatic and portal veins and the common bile duct, readily apparent on injection of the aorta with barium sulfate, which are more difficult of removal. Further, adhesions form to the new operative sites necessary in multiple stage operations. The amount of arterial blood entering the liver after removal of the hepatic and phrenic supply must, however, be small.

The oxygen determinations on the blood of the portal and hepatic veins clearly show that further reduction of portal blood occurs in the liver.

CONCLUSIONS

In dogs, ligation of the hepatic artery and its largest collaterals, the gastroduodenal and the right gastric artery, in one stage was fatal. Preliminary ligation of the hepatic artery proximal to this point of anastomosis was never fatal and permitted subsequent ligation of collaterals, including the phrenic and cystic arteries.

After subtotal arterial removal in stages, no histologic or physiologic abnormalities were detected in the liver. Acute cholecystitis frequently developed.

The liver is able to utilize oxygen from the blood of the portal vein.

Prof. E. S. Guzman Barron made the determinations of blood oxygen.

LYMPHOID HYPERPLASIA OF THE APPENDIX

WITH A NOTE ON ITS ROLE IN ACUTE APPENDICITIS

S. H. GRAY, M.D.
AND
CARL J. HEIFETZ, M.D.
ST. LOUIS

In the routine examination of appendixes removed at operation we were impressed by the unusual richness of the lymphoid tissue as the prominent histologic feature in a group of cases presenting the clinical syndrome of a mildly acute, subacute or recurrent appendicitis. Our studies led us to believe that hyperplasia of lymphoid tissue, either focally or diffusely, may cause sufficient obstruction in the narrow-lumened appendix to produce symptoms simulating appendicitis. Furthermore, in reviewing a series of cases of pathologically early acute appendicitis, we felt that here, too, the hyperplasia of the lymphoid tissue might be a factor of prime etiologic importance.

Lymphoid hyperplasia of the appendix has been described by Wätzgold,[1] Klemm,[2] Miloslavich,[3] Stout,[4] Moschcowitz,[5] Barss,[6] Symmers and Greenberg[7] and Smith.[8] Most of these investigators considered it a phase of status lymphaticus. Smith thought that it constituted a definite clinical entity.

Since all gradations in the amount and activity of the lymphoid tissue in the appendix may be present both in the same person and in different

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From the Laboratory of the Jewish Hospital.

This work was aided by a gift in memory of Mrs. Carrie Scott Johnson.

1. Wätzgold: Beitrag zur pathologischen Anatomie des Wurmfortsatzes unter besonderer Berücksichtigung der Ausheilungserscheinungen der Appendicitis acuta, Beitr. z. path. Anat. u. z. allg. Path. **42**:260, 1907.

2. Klemm, P.: Ueber die Erkrankung des lymphatischen Gewebes und ihr Verhältnis zur Appendicitis, Deutsche Ztschr. f. Chir. **81**:427, 1906.

3. Miloslavich, E.: Zur Pathogenese der Appendizitis, Wien. klin. Wchnschr. **25**:442, 1912.

4. Stout, A. P.: Isolated Lymphoid Hyperplasia in the Cecum and Appendix of Children, Am. J. Dis. Child. **34**:797 (Nov.) 1927.

5. Moschcowitz, E.: The Pathological Diagnosis of Diseases of the Appendix Based on the Study of 1,500 Specimens, Ann. Surg. **63**:697, 1916.

6. Barss, H. deB.: Lymphatic Disease in Children Simulating Appendicitis, Am. J. Dis. Child. **15**:421 (June) 1918.

7. Symmers, D., and Greenberg, M.: Clinical Significance of Lymphoid Hyperplasia of the Appendix, J. A. M. A. **72**:468 (Feb. 15) 1919.

8. Smith, T. A.: Lymphoid Hyperplasia of the Appendix in Children, Ann. Surg. **79**:871, 1924.

persons, it was necessary to establish some arbitrary standard by which we could select our cases of lymphoid hyperplasia. We included in our study only those appendixes with one half or more of the entire wall composed of lymphoid tissue. In addition, the follicles exhibited definite signs of hyperactivity, as shown by an increase in the size of the germinal centers and the presence of mitoses, phagocytosis and dilatation of the lymphatics in the muscular and serosal coats.

The appendixes were fresh when brought to the laboratory. Cross-sections were made usually proximal to the middle and near the tip. The site of a single section, as far as could be ascertained, was distal to the middle. When tissue was available, more sections were cut. The tissue was fixed in a solution of formaldehyde.

In the years 1926 to 1933 inclusive, there were approximately fourteen hundred appendectomies performed at the Jewish Hospital. We have examined the records of all these cases and have uncovered fifty-one in which a definite diagnosis of lymphoid hyperplasia of the appendix could be made. No cases in which the diagnosis was doubtful are included in our series.

The data on these cases are presented in the following outline:

I. Incidence

Sex: Male.....15 Female.....36

Age:		
1 to 5..... 2	21 to 25.....11
6 to 10..... 6	26 to 30..... 2
11 to 15.....14	31 to 35..... 1
16 to 20.....15	

Average age: 17 Lowest age: 3 Highest age: 35

II. History

Duration of attack (on admission):

Over 3 days.....	23
1 to 3 days.....	9
Less than 24 hours.....	19

	Present	Absent	Not Recorded
Nausea	35	13	3
Vomiting	23	25	3
Constipation	11	29	11
Previous attacks	28	19	4
Symptoms of infection of the upper respiratory tract	13	17	21

III. Physical Findings

	Marked	Moderate	Slight	Absent	Not Recorded
Tenderness	10	27	13	1	0
Rigidity	2	7	21	21	0
Rebound tenderness.....	1	0	13	24	13
Meltzer's sign.....	0	8	10	20	13

Rectal temperature (on admission):

Below 100 F.	27
100 to 100.8 F.	18
101 to 101.8 F.	4
102 F. and over	2

Highest temperature: 103.8 F.

Leukocyte count:

4,000 to 6,000	3	12,000 to 14,000	12
6,000 to 8,000	11	14,000 to 16,000	10
8,000 to 10,000	16	16,000 to 19,000	2
10,000 to 12,000	14		

Average count..... 10,350 Maximum count..... 18,800

Minimum count..... 4,650

The seventeen extra leukocyte counts were those repeated on several patients during their preoperative stay in the hospital.

Differential count: A Schilling differential count was done in eleven cases. In only one case was there a relative increase in the neutrophilic cells. In four cases there was a shift to the left. In none of the cases was there lymphocytosis. The average leukocyte count was 9,800.

IV. Preoperative Diagnosis:

Acute appendicitis	22
Subacute appendicitis	17
Chronic appendicitis	2
Recurrent appendicitis	10

V. Postoperative Course:

In nearly all cases the postoperative course was uneventful. There was infection of the wound in one. One patient died a year later of acute myelogenous leukemia.

To summarize the foregoing data briefly, we are confronted with a picture hardly distinguishable from that of mild appendicitis. The patients, twice as often female as male and most often adolescents or young adults, entered the hospital after having had one or more attacks of pain in the right lower abdominal quadrant. The pain was usually cramplike or dull but sometimes quite sharp and colicky, and in several cases it was of such severity as to make the patient "double up." It lasted anywhere from several hours to several days, and as a general rule the longer its duration, the less its severity. The pain remained localized in this area and never radiated. Sometimes there was a remission and then a recurrence. In most cases there was a history of previous attacks of similar pain. Pain was the only symptom that was always present, and its location immediately centered the attention of the surgeon and frequently that of the patient on the appendix. Nausea was usually present. Vomiting occurred in half the cases at some time during the course of the illness. Constipation was present in about a fourth of the cases. Some mention of signs or symptoms referable to the upper

respiratory tract, such as a cold, a sore throat, rhinitis and pharyngitis, was made in about a third of the cases.

On physical examination tenderness of varying degrees, but usually moderate, was always present. Slight rigidity was generally present. Rebound tenderness and a positive Meltzer sign were inconstant. A slight elevation of temperature was often present when the patient was admitted to the hospital. It was noticed that in some of these cases the fever subsided when the patient was put to bed for a day or two. If any figure up to 10,000 is considered as a normal leukocyte count for this age period, we find that in slightly more than half the cases there was a mild leukocytosis. The few Schilling hemograms taken gave inconstant values.

The patients went to operation with a certain or likely diagnosis of acute, subacute or recurrent appendicitis. The appendixes were described grossly as being anywhere from "normal" to "bound down by adhesions." A frequent notation was the presence of congested vessels in the subserosa. The operative report on three cases mentioned enlarged ileocolic lymph nodes.

We have not made any attempt to locate these patients to determine if symptoms persisted postoperatively, but the occasional patient whom we have subsequently encountered has been almost entirely free from a recurrence of symptoms. One complained of some slight pain similar to that experienced before operation but less severe.

It may be of interest to summarize briefly the observations of previous investigators. Barss [6] in 1918 reported a syndrome strongly suggestive of recurrent attacks of appendicitis in seven children, i. e., localized nonradiating pain in the right lower abdominal quadrant lasting from several hours to several days, usually accompanied by nausea but rarely by vomiting. Constipation and headache were frequent symptoms. There was no fever or leukocytosis. The only constant physical sign was localized tenderness. Muscle spasm was absent in most cases. At operation, enlarged mesenteric lymph nodes were usually found. The notable change microscopically was hyperplasia of the lymphoid tissue of the appendix. The author ventured the opinion that this might be one of the manifestations of "status lymphaticus."

Symmers and Greenberg [7] examined several thousand appendixes at the Bellevue Hospital and noticed that lymphoid hyperplasia was the sole pathologic change in 10 per cent. A study of twenty typical cases, ten in males and ten in females, was made. The average age was 17½ years. There was a history of from two to eight attacks of pain lasting several hours or days, referable to the region of the appendix. The temperature, pulse and leukocyte count were usually normal. Constipation, headache and nausea were frequent, and vomiting was rare. The

authors attributed this condition to the instability of the lymphatic system generally associated with a mild "status lymphaticus."

Smith [8] reviewed thirty-seven cases occurring in a period of eight years in children under 12½ years in the children's surgical service at the Bellevue Hospital. Twenty-two cases occurred in girls and 15 in boys. All the patients gave a history of colicky pain, often intermittent, starting about the umbilicus and later localizing in the right iliac region. Three fourths gave a history of previous attacks. Two thirds had symptoms of nausea and vomiting. Localized tenderness was present in all, and rigidity of some degree was present in one half. A slight elevation of temperature was frequently noted on the patient's admission, but usually subsided when he was put to bed. The average leukocyte count in twenty-nine cases was 10,700, which the author considered normal for this age period. There were, however, seven cases in which the leukocyte counts ranged between 12,000 and 15,000. All patients had satisfactory postoperative courses. Thirty-one were followed for periods of from three months to six years, and except for two, were entirely free from further abdominal symptoms.

PATHOLOGIC PICTURE

On gross examination of an appendix with lymphoid hyperplasia the usual findings of an acute inflammatory process are absent. The serosa is pale, shiny and smooth, and the wall is moderately thickened. On cross-section the lumen is quite diminished in size and sometimes is almost occluded. Frequently it has a slitted or stellate appearance. The lumen may vary in shape and size in the same appendix. Slight pressure near the cut end pushes out the mucosa and submucosa and demonstrates that these layers occupy more than half the wall. The hyperplastic lymph follicles can be seen in bright daylight as small yellow or pink areas the size of a pinpoint, some of which produce distinct elevations of the mucosa.

Microscopically, the most notable change is the absolute and relative increase in the amount of lymphoid tissue, evidenced chiefly by the large lymph follicles (fig. 1). The lymphoid tissue frequently occupies as much as three fourths of the wall. The individual follicles are considerably enlarged. Their normal spherical shape tends to become ovoid, the long diameters being arranged radially around the lumen. The contour of the latter is largely determined by the size, shape and arrangement of these follicles. Occasionally two adjacent follicles have so elevated their overlying mucous membrane as to leave a deep cryptlike depression between the two swellings (fig. 2). The same appendix may, in different sections, show hyperplastic follicles, normal follicles or both. Of course one must always bear in mind that many follicles are sectioned eccentrically and hence give the appearance of normal size.

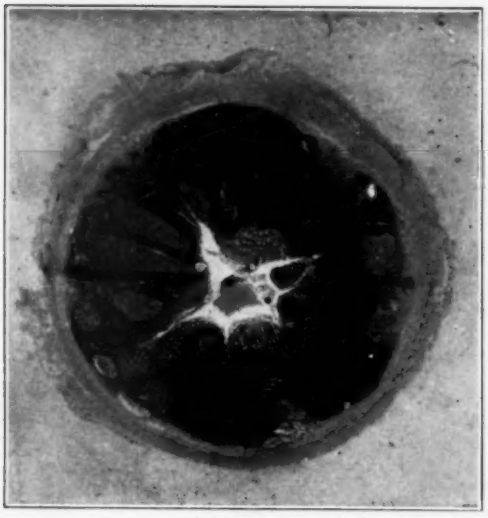

Fig. 1.—Cross-section of an appendix showing hyperplasia of the lymphoid tissue, which occupies well over half the wall. The hyperplastic follicles consist chiefly of germinal centers. Hematoxylin and eosin stain; × 7.

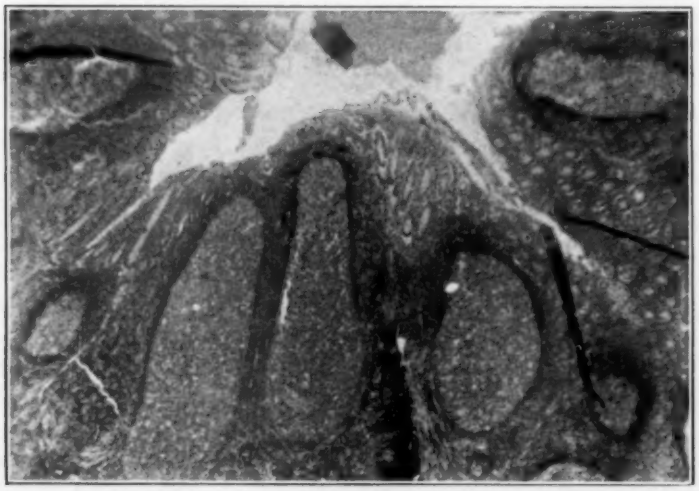

Fig. 2.—Crypt formation between hyperplastic lymph follicles. Hematoxylin and eosin stain; × 25.

The lymph follicles are in a state of hyperactivity. Each follicle contains a large light central area, the germinal center, surrounded by a thinner zone of denser hue. The germinal center (fig. 3) is composed of large, loosely arranged, somewhat irregular cells. Most of these are reticulum cells, the nuclei of which stain lightly and contain small amounts of finely stippled or strandlike chromatin, a dense, almost black, irregular nucleolus and a fine nuclear membrane. The remainder of the cells are chiefly large and medium-sized lymphocytes. Occasionally one sees a cell which seems to be transitional from the reticulum cell to the large lymphocyte. Mitoses are fairly common. Tissue eosinophils and plasma cells are rare. Other changes in the

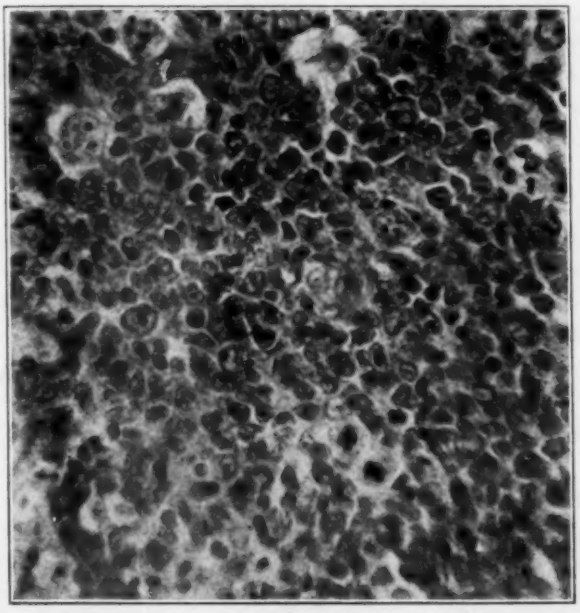

Fig. 3.—Section through the germinal center of a hyperplastic lymph follicle, showing several mitotic figures and phagocytic cells containing fragments of ingested nuclear débris. Hematoxylin and eosin stain; × 400.

germinal centers include rare tissue macrophages with phagocytosed nuclear material and some pyknotic nuclear material. This phagocytosis is probably not above physiologic limits. Polymorphonuclear cells are almost completely absent. The outer zone of the follicles consists of densely packed, more uniform and medium-sized lymphocytes. The changes present are more indicative of an active physiologic process than of a toxic or destructive lesion. No changes are present which cannot be duplicated in normal secondary lymph nodules at one time or another. The differences from the normal lymph follicle are quantitative rather than qualitative.

We have measured typical examples of hyperplastic lymph follicles and have found many to measure well over 1.5 mm. in diameter. The largest follicle measured 2.25 by 1.75 mm. However, they usually averaged slightly more than 1 mm. in their longer diameters and slightly less than 1 mm. in their shorter diameters.

COMMENT

Liebeck [9] has shown that the lymphoid follicles occupy about 30 per cent of the mucosal surface of the appendix. The variations lie between 8.2 and 52.8 per cent. Changes with age in the amount of lymphoid tissue do not correspond entirely with changes in the size of the appendix as a whole. The appendix grows only slightly from birth to adolescence. From puberty to the age of 35 years its size is usually constant.[10] The lymphoid tissue, however, increases at a slightly greater rate than the appendix as a whole, so that the greatest amount of lymphoid tissue, both relatively and absolutely, is present between 17 and 35 years.[11] In this respect, the lymphoid tissue of the appendix differs from that of the remainder of the body. Whitney [12] has shown that the lymphoid tissue in general reaches its relative maximum during the ages of 2 to 5. After this period there is a gradual decrease until adolescence, when there is a sudden decrease in the relative amount of lymphoid tissue. The total amount of lymphoid tissue by weight, however, shows a gradual increase until adolescence, when it reaches a constant level, which is maintained until about the twenty-fifth year of life.

The peak of the number of follicles in the appendix is present between 10 and 20 years.[13] At this stage the follicles vary between 0.8 and 1 mm. in diameter. The number of follicles in the appendix is estimated by Berry and Lack [14] at 200 and by Keeley and Hundin [15] at from 300 to 400. The lymphoid tissue increases in density toward the tip.[16]

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9. Liebeck, cited by Berry and Lack.[14]

10. Nowicki, W.: Anatomische Untersuchungen über Appendix und Appendizitis, Virchows Arch. f. path. Anat. **195**:177, 1909.

11. Shiota, H.: Ueber das Verhalten des Wurmfortsatzes bei Lymphatismus, Wien. klin. Wchnschr. **22**:1101, 1909.

12. Whitney, C.: Hyperplasia of Lymphoid Tissue and Lymphocytosis, Medicine **7**:1, 1928.

13. Nagoya, C.: Ueber die Drüsen und die Follikel des Wurmfortsatzes, Frankfurt. Ztschr. f. Path. **14**:106, 1914.

14. Berry, R. J. A., and Lack, L. A. H.: The Vermiform Appendix of Man, and the Structural Changes Therein Coincident with Age, J. Anat. & Physiol. **40**:247, 1905-1906.

15. Keeley and Hundin, cited by Berry and Lack.[14]

16. Wätzgold.[1] Berry and Lack.[14]

Several factors seem to stimulate the lymphoid tissue. That most frequently emphasized is infection, against which the tissue constitutes a defensive mechanism for the body.[17] Responses to physical and chemical irritations have been noted.[12] Many observations tend to show that lymphoid tissue, particularly that along the alimentary canal, is greatly concerned with the metabolism of fat [18] and during this function may undergo hyperplastic changes. Bunting [19] expressed the belief that there is a variation in the resistance of the lymphoid tissue, depending on age and sex. He found that the lymphatic system is most susceptible to injury in the immediate postpuberty years, with the male less resistant than the female.

The most characteristic response of lymphoid tissue to any agent is hyperplasia. This response may result not only from toxic and physical agents but from physiologic activity. Progressive and retrogressive changes in activity are constantly occurring during the regular stresses and strains of physiologic activity. Frequent swelling of the lymph glands of an insidious nature come and go without an obvious etiologic agent. Although the various lymphoid organs and lymph follicles tend to be interdependent and interresponsive, hyperplastic changes may occur at a site entirely remote from the original focus of stimulation. Thus it is entirely possible for focal hyperplasia to occur without similar involvement elsewhere.[20] The lymphatic system as a whole is very labile, unpredictable and variable in its systemic and local response. Given a certain etiologic agent, either pathologic or physiologic, and the response may be a generalized lymphatic reaction or one confined locally or remotely.

The vermiform appendix is largely a lymphoid organ. Hence its lymphoid response is subject to the same variations and etiologic factors as lymphoid tissue elsewhere. The association of mild appendical symptoms with acute infections of the upper respiratory tract has been frequently noted.[21] Along with, or independent of, other lymphoid

17. Beitzke, H.: Ueber den lymphatischen Rackenring und seine Rolle als Eintrittspforte von Infektionen, Wien. klin. Wchnschr. **39**:1473, 1926. Whitney.[12]

18. (*a*) Dudgeon, L. S., and Mitchiner, P. H.: Bacteriological and Pathological Examination of the Vermiform Appendix in the First Thirty Hours of Acute Appendicitis, Brit. J. Surg. **11**:676, 1924. (*b*) Lefholz, R.: The Effect of Diets Varying in Caloric Value and in the Relative Amounts of Fat, Sugar, and Protein upon the Growth of Lymphoid Tissue in Kittens, Am. J. Anat. **32**:1, 1923. (*c*) Settles, E. L.: The Effect of High Fat Diet upon the Growth of Lymphoid Tissue, Anat. Rec. **20**:61, 1921.

19. Bunting, C. H.: Variations in Lymphoid Resistance, Tr. A. Am. Physicians **41**:30, 1926.

20. Stout.[4] Nagoya.[13]

21. Brennemann, J.: "The Abdominal Pain in Throat Infection in Children" and Appendicitis, J. A. M. A. **89**:2183 (Dec. 24) 1927. Lowenstein, P.: Respiratory Diseases That Mimic Appendicitis, J. Missouri M. A. **29**:563, 1932.

organs, the follicles of the appendix may undergo hyperplastic changes, either all or only a few of the follicles being involved. Follicles may be involved at the tip or at the base; a group may become hyperplastic on one side of the lumen or on the other. After the inciting agent is removed or successfully overcome, the follicles may return to normal. These changes are constantly at work in the appendix as in other lymphoid structures. We feel that clinical symptoms result from the response of the lymphoid tissue in a narrow-lumened organ to these variable stimuli. This usually occurs during the period in life when the lymphoid tissue is normally at its richest.

Our choice of fifty-one appendixes may be considered arbitrary. It so happens that in these the process was shown to the best advantage in the chance sections obtained. It is likely that many other appendixes showed similar undiscovered processes at the time they were removed. In fact, it would be logical to assume that most appendixes undergo some lymphoid hyperplasia at one time or another, it being physiologic and asymptomatic in a large majority.

The relationship between lymphoid hyperplasia of the appendix and status lymphaticus that previous workers have stressed we think unwarranted. Hart [22] wrote in 1923:

> The doctrine of Status Thymico-Lymphaticus has shared the fate of so many other doctrines. Only reluctantly adopted at first by medical men, it has become more and more the prey of uncritical application and exaggeration and at last a great receptacle for everything (zu einem grossen Sammelbecken geworden) into which every conceivable morphological and functional appearance is thrust, so practically the whole field of pathology is covered by the Status Thymico-Lymphaticus. It is, to use an expression of Pfaundler's, denatured into a "pandiathesis."

More recently, the report of a comprehensive survey by the Status Lymphaticus Committee [23] ended with the sentence:

> In the opinion of the committee the facts elicited in the present inquiry were in harmony with those of Hammer (1926 and 1929) and Greenwood and Woods (1927) in affording no evidence that so-called "status thymico-lymphaticus" has any existence as a pathological entity.

The mechanism of pain and nausea in our cases of lymphoid hyperplasia probably is similar to that in cases of acute appendicitis. Morley [24]

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22. Hart, cited by Greenwood, M., and Woods, H. M.: "Status Thymico-Lymphaticus" Considered in the Light of Recent Work on the Thymus, J. Hyg. **26**:305, 1927.

23. Young, M., and Turnball, H. M.: An Analysis of the Data Collected by the Status Lymphaticus Committee, J. Path. & Bact. **34**:213, 1931.

24. Morley, J.: Abdominal Pain as Exemplified in Acute Appendicitis, Brit. M. J. **1**:887 (May 26) 1928.

expressed the belief that appendical pain has two components. The initial pain varies in intensity but is usually dull and spasmodic and often accompanied by nausea. Tenderness is not marked, and rigidity is usually absent. This pain is due to increased tension on the muscular wall. Hertz [25] and Ryle [26] have experimentally shown that increased tension on the muscular wall of a hollow viscus results in similar pain. Obstruction to the lumen is a factor, since it also increases the muscular tension. The secondary pain occurs later and is much sharper and better localized; more tenderness is present, and there is definite rigidity. This pain is due to extension of the process to the peritoneum.

It is the initial type of pain which we recognize as occurring in lymphoid hyperplasia. The secondary type is notably absent. The swelling of the lymph follicles might produce the same tendency to stretch the muscular wall as an acute inflammatory swelling of the mucosa and submucosa. The lumen of the appendix is normally small, and the wall is quite rigid. In many cases hyperplasia of several follicles would be sufficient to occlude the lumen enough to result in stasis, causing forceful propulsive muscular contractions behind the occlusion. The occlusion may also be assisted by the presence of inspissated feces or other material. It is not necessary for the entire appendix to become involved in this process. One small occlusive process would be sufficient. In this respect the appendix differs from, for instance, the ileum. In the latter organ no degree of lymphoid hyperplasia of Peyer's patches would be productive of a similar occlusion or even stretching of the muscular wall. Smith [8] mentioned that at least some of the pain from appendical lymphoid hyperplasia is due to stretching of the serosa resulting from swelling of the follicles.

The occasional presence of leukocytosis needs a few words of comment. In the age group considered here the variability of leukocyte counts is sufficient to make the establishment of a definite maximum level of normal difficult. The few counts that are distinctly elevated may be due to the presence of some mild unrecognized intercurrent infection. It is possible, of course, that this intercurrent infection may also invite, in addition to the usual defensive mechanisms of the body, the hyperplastic response of lymphoid tissue. Fever falls in the same category. Many patients on first entering the hospital show an initial unexplained slight elevation of temperature.

It is also conceivable that many of these instances of lymphoid hyperplasia, especially those in which leukocytosis or fever is present, may be

25. Hertz, A. F.: The Goulstonian Lectures on the Sensibility of the Alimentary Canal, London, H. Frowde, 1911.

26. Ryle, I. A.: Visceral Pain and Referred Pain, Lancet **1**:895 (May 1) 1926.

aborted cases of very mild acute appendicitis in which the minute lesion was not found. This concept takes on definite possibilities, from the evidence we have gathered, that lymphoid hyperplasia may be an important etiologic factor in the production of acute appendicitis.

The early years of the present century were productive of two main theories of origin of acute appendicitis. Kretz [27] was an early advocate of the hematogenous (from the tonsils) origin of acute appendicitis, and his supporters were many.[28] Aschoff [29] formulated the enterogenous theory of origin, in which he described the earliest stages of acute appendicitis originating in the depths of the mucous crypts and spreading through the walls from this original focus. The intervening years have seen numerous battles between these two schools, but more recently the evidence on the side of Aschoff has become so great that most observers at present favor the enterogenous theory.[30] We, too, adhere to Aschoff's concept so far as the original site and spread of the infection are concerned. But we venture to go back one step and state that hyperplasia of the lymph follicles may be responsible for the deepening of the crypts and for the closing off of their free connection with the main lumen, thereby promoting stasis in the depths of the crypts. A comparable process occurs in acute tonsillitis. This concept of the origin of acute appendicitis also conforms with repeated and well substantiated observations that acute appendicitis has some relationship to generalized infections,[31] observations on which much of the hematogenous theory

27. Kretz, R.: Studies on the Etiology of Appendicitis, Internat. Clin. **3**:285, 1908.

28. Anderson, H. B.: Appendicitis as a Sequela of Tonsillitis, Am. J. M. Sc. **150**:541, 1915. Chase, C.: The Etiology of Appendicitis, Am. J. Obst. **73**:444, 1916. McCoy, F. C.: The Rôle of the Tonsil in the Production of Appendicitis, Lancet-Clinic **116**:49, 1916. Poynton, J., and Paine, A.: A Further Contribution to the Study of the Etiology of Appendicitis as a Result of Blood Infection, Lancet **2**:439, 1912. Wilkie, P. D.: The Etiology of Acute Appendicular Disease, Canad. M. A. J. **22**:314, 1930.

29. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908.

30. Böhne, Carl: Untersuchungen zur Pathogenese der Wurmfortsatzentzündung, Arch. f. klin. Chir. **171**:692, 1932. Kühnel, P.: Some Examinations of the Local Eosinophilia in the Vermiform Appendix, Acta chir. Scandinav. **53**:476, 1920-1921. McMeans, J. W.: Experimental Appendicitis, Arch. Int. Med. **19**:709 (May) 1917. Riff, A.: Contribution à l'étiologie de l'appendicite, Presse méd. **27**:521, 1919. Steinberg, B.: Degenerative Lesions of the Appendix, Am. J. Clin. Path. **1**:339, 1931. Warren, S.: The Etiology of Acute Appendicitis, Am. J. Path. **1**:241, 1925. Wätzgold.[1] Moschcowitz.[5]

31. Armstrong, A. W.: The Causes of Appendicitis, New York M. J. **87**:66, 1908. Evans, J. S.: Epidemiology of Acute Appendicitis in Relation to Acute Nasal and Tonsillar Infections, Wisconsin M. J. **17**:91, 1918. Herzberg, M.: Giant Cells in the Lymphoid Tissue of the Appendix in the Prodromal Stage of

(Footnote continued on next page)

of the origin of acute appendicitis rests. This relationship may well be through the general lymphatic system, the appendical lymphoid tissue playing a rôle in this by becoming hyperplastic. Thus it is possible to reconcile the enterogenous and hematogenous theories through the intermediacy of the lymphoid tissue of the appendix.

Statistics show that acute appendicitis occurs most frequently in the postpuberty years and early adulthood.[32] A glance at our figures shows that our cases of lymphoid hyperplasia fall into the same age groups. This is the period of life when the lymphoid tissue is normally richest. These facts seem significant.

The infrequency of appendicitis in such countries as China, India, Arabia and Africa, where careful observations on the native populations show them to be practically immune to this disease, has never been adequately explained. Most investigators agree that the most important factor is diet.[33] From the data we have been able to obtain the chief difference in diet is a lower consumption of protein and fat in these countries. In the past the protein factor was held responsible, although its mode of action was not known. If we consider the fat factor, however, in the light of the experiments of Settles[18c] and Lefholz,[18b] who have shown that prolonged fat diets produce hyperplasia of lymphoid tissue, we have here a possible linking of diet and acute appendicitis through the lymphatic system.

Measles: Report of Isolated Case, J. A. M. A. **98**:139 (Jan. 9) 1932. Hunt, W. M.: The Relation Between Tonsillitis and Appendicitis, Am. J. Surg. **6**:761, 1929. Watson-Williams, P.: Nasal Sinus Infections as a Causal Factor in Appendicitis, Practitioner **106**:229, 1921.

32. Bancroft, F. W.: Acute Appendicitis: A Review of Five Hundred and Eighty-Four Consecutive Cases, J. A. M. A. **75**:1635 (Dec. 11) 1920. Beekman, F.; Smith, M. K., and Everingham, S.: Acute Appendicitis: An Analysis of Five Hundred Cases, Am. J. M. Sc. **154**:490, 1917. Flint, E. R.: Acute Appendicitis: A Study of Three Hundred and Seventy Cases, Practitioner **104**:352, 1920. Keyes, E. L.: Death from Appendicitis, Ann. Surg. **99**:47, 1934. Maylard, A. E.: Sex and Age Incidence in Appendicitis, Brit. J. Surg. **8**:189, 1920.

33. Crichlow, N.: A Case of Appendicitis in a Native of the Solomon Islands, Western Pacific, J. Trop. Med. **23**:22, 1920. Gibson, R. M.: The Incidence of Appendicitis in Chinese, China M. J. **40**:43, 1926. Mantle, A.: The Cause of Appendicitis, Brit. M. J. **1**:399, 1911. Reyes, C.: Appendicitis Among Filipinos, J. Philippine Islands M. A. **5**:75, 1925. Shaheen, H. I.: The Cause of Appendicitis, Brit. M. J. **1**:165, 1911. Waller, H. W. L.: A Case of Acute Appendicitis in a Native of Africa, J. Trop. Med. **22**:1, 1919. Weischer, P.: Ueber Perityphlitis bei Chinesen, Zentralbl. f. Chir. **50**:875, 1923. Williams, O. T.: Microchemical Changes Occurring in Appendicitis, with a Note on the Incidence of the Disease in Various Countries, Biochem. J. **3**:391, 1908.

CONCLUSIONS

Lymphoid hyperplasia of the appendix was found in fifty-one of a group of fourteen thousand appendixes.

The clinical symptoms presented simulated those of mild acute appendicitis.

The clinical picture is explained on the basis of an obstruction by hyperplasia of lymphoid follicles in a narrow-lumened organ, occurring during a period of life when the lymphoid tissue is normally richest.

A theory is presented indicating the possible etiologic relationship between lymphoid hyperplasia and acute appendicitis.

THE ADRENAL CORTEX

A CYTOLOGIC STUDY OF NORMAL AND OF PATHOLOGIC TISSUE

E. LEE STROHL, M.D.
Fellow in Surgery, the Mayo Foundation
ROCHESTER, MINN.

The adrenal gland was first described by Eustachius [1] in 1564 and the adrenal medulla, by Bartholin [2] in 1666. The adrenal gland of man, as such has been the object of considerable study in the past. These studies, however, have been directed primarily to the chemical nature of the cells of both the cortex and the medulla. Various workers who have dealt with pathologic adrenal tissue have stressed the cell unit rather than the individual components of the cell.

Study of malignant cells indicates that there is an absence of normal differentiation, specific function and intercellular organization. It is to these characteristics that Hansemann [3] applied the term "anaplasia" in his early publications. Anaplasia is associated with changes in the morphologic characteristics of the cells; such changes occur to a lesser degree in association with reparative regenerative hyperplasia and in benign cells. Because of morphologic gradations, the approach to an early diagnosis of a malignant process must be made by careful study of the individual cell and its individual parts.

For more than fifty years there has been a constant attempt to recognize cytologic differences which might aid in the differential diagnosis of malignant conditions. Stenius [4] in 1925 observed a relative increase in the size of the nucleoli of malignant cells in urinary sediment, and

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Abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Eustachius, cited by Stöhr, P., and Lewis, F. T.: A Textbook of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913, p. 404.

2. Bartholin, cited by Stöhr, P., and Lewis, F. T.: A Textbook of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913, p. 404.

3. Hansemann, David: Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung, Virchows Arch. f. path. Anat. **119**:299-326 (Feb. 4) 1890.

4. Stenius, Fjalar: Zur Bewertung des epithelialen Harnsedimentes für die Diagnose der Blasengeschwülste, Acta chir. Scandinav. **58**:240-255, 1925.

studies conducted by Aichel,[5] Hertwig,[6] Heiberg [7] and others attempted to establish such criteria for the diagnosis of malignant processes. They studied the relationship between nuclei and cytoplasm and stated that the low nucleoprotoplasmic ratio, which at first was thought to be characteristic of malignant cells, was also present in embryonic cells and that such cells merely represent rapid growth and cell division.

Many years ago MacCarty [8] observed a marked difference in the relative size of the nuclei and nucleoli of benign as compared to malignant cells. In 1924 he published his first articles dealing specifically with this phase of the subject, although his earlier studies had suggested a difference in the size of the nucleoli in regenerative and in malignant cells. Since that time studies have been made on tissue from the breast, large intestine, lymph nodes, uterus and stomach by MacCarty and his colleagues, Haumeder and Berkson,[9] and by McCormack [10] and Naidu.[11] Such a comprehensive cytologic study has not been conducted heretofore on the adrenal gland. It is a well known fact that tumors of the adrenal gland are an uncommon finding, both clinically and pathologically. However, a sufficient number of these tumors have been encountered at the Mayo Clinic so that such a study could be carried out. It is the purpose of this paper, therefore, to present the data for both normal and pathologic adrenal cortex.

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5. Aichel, cited by Sokoloff, Boris: The Nucleo-Cytoplasmic Ratio and Cancer, J. Cancer Research **7**:395-415 (Oct.) 1922.

6. Hertwig, R.: Ueber Korrelation von Zell- und Kerngrösse und ihre Bedeutung für die geschlechtliche Differenzierung und die Teilung der Zelle, Biol. Centralbl. **23**:49 and 108, 1903.

7. Heiberg, K. A.: Studien über Haut-Epithel-Atypie bei Krebs- und Granulationsgewebe und die diagnostische Verwendung der Kerngrösse, Virchows Arch. f. path. Anat. **234**:469-480, 1921.

8. MacCarty, W. C.: Studies in the Etiology of Cancer: IV. Notes on the Regularity and Similarity of Cancer-Cells, in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1914, vol. 6, pp. 600-602; A Biological Conception of Neoplasia: Its Terminology and Clinical Significance, Am. J. M. Sc. **157**:657-674 (May) 1919; The Cytologic Diagnosis of Neoplasms, J. A. M. A. **81**:519-522 (Aug. 18) 1923; The Early Diagnosis of Cancer, Arch. Clin. Cancer Research **1**:11-20 (Jan.) 1925.

9. MacCarty, W. C.; Haumeder, Eva, and Berkson, Joseph: A Differential Characteristic of Malignant Cells: Preliminary Report, Proc. Staff Meet., Mayo Clin. **8**:38-45 (Jan. 18) 1933. MacCarty, W. C., and Haumeder, Eva: Has the Cancer Cell Any Differential Characteristics? Am. J. Cancer **20**:403-407 (Feb.) 1934.

10. McCormack, C. J.: Biometric Studies of Endometrial Cells, Proc. Staff Meet., Mayo Clin. **10**:24-29 (Jan. 9) 1935.

11. Naidu, V. R.: The Value of Enlarged Nucleoli in the Diagnosis of Malignancy, Proc. Staff Meet., Mayo Clin. **10**:356-362 (June 5) 1935.

METHOD OF STUDY AND MATERIAL USED

Tissue from normal and renal cortices that were removed at necropsy was placed in a solution of formaldehyde. Frozen sections were made after twenty-four hours and stained with hematoxylin. In unfixed specimens of tissue, tracings of the cells were made within a few minutes after removal of the tissue from the living body in order that the cells would not have been altered. With an oil immersion lens and a Spencer microscope (objective, 1.8 mm.; numerical aperture, 1.25; length of tube, 150 mm.; ocular, 10×), the nuclei and the nucleoli of 20 cells from different parts of each section were projected by means of a camera lucida on paper and then were traced. The tracings of the nuclei and nucleoli were measured directly by a planimeter to obtain their areas. The tracings of nucleoli were necessarily further enlarged to obtain measurable areas; this was done by means of a camera lucida and a Spencer microscope (objection, 48 mm.; length of tube, 250 mm.; ocular, 1×). The areas of the nuclei and nucleoli were then corrected to allow for the foregoing magnifications as well as for the planimeter constant. The final true areas of the nuclei and nucleoli were expressed in square microns. Throughout this work care was taken to keep the length of the tube constant, frequent checks being made so that the areas of nuclei and nucleoli from comparable sections were recorded.

The specimens of pathologic tissue were removed at operation. This tissue was studied in essentially the same manner as the normal tissue. The results obtained should be considered only after the embryology, anatomy, histology and pathology of the adrenal cortex are understood. I shall attempt to discuss them briefly.

NORMAL ADRENAL CORTEX

Embryology and Anatomy.—The adrenal gland, of course, has a double origin, but as I am dealing with the cortex I shall discuss only that portion of the gland.

The anlage of the cortex is first noticed in the embryo of 6 mm., wherein a bud projects from the peritoneal mesothelium near the root.[12] In the embryo of 9 mm. these cells have migrated to their positions above each kidney. A differentiation into the mature type of gland does not occur until the end of the third year.[13] At the end of the third month, and in the first half of the fourth month, the gland is larger than its contiguous kidney. At the sixth month it has decreased to one-half, and at birth to one-third, the size of the kidney; in the adult the ratio of the size of the adrenal gland to the kidney is 1 : 28.[14] The weight of the gland varies from 6 to 7 Gm., the left one being slightly larger that the right. The gland lies above the kidney and has the gross appearance of a cocked hat. Its surface is slightly yellow, and the gland seems to be rather densely adherent to the surrounding structures. Frequently the gland is adjacent to the

12. Morris, H.: Human Anatomy, ed. 9, edited by C. M. Jackson, Philadelphia, P. Blakiston's Son & Co., 1933.

13. Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text-Book of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1920.

14. Piersol, G. A.: Human Anatomy, ed. 2, Philadelphia, J. B. Lippincott Company, 1923, p. 1801.

upper pole of the kidney, the whole having the appearance of being a single structure until close examination reveals a definite difference in tissue. Accessory adrenal tissue is a relatively common anatomic finding, and that found in the broad ligament of the female has been given the name "Marchand's adrenal." Accessory adrenal tissue has been reported in association with every tissue or structure below the diaphragm; usually only cortical tissue is found. As many as 50 per cent of new-born infants will be found to have accessory adrenal tissue if closely studied. Because of the common ancestry of the adrenal gland, testis and ovary, disturbances of these glands are prone to produce heterosexual changes. Removal of adenoma of these glands causes a reversion to normal status.[15]

Histologic Structure.—By the end of the third year the adrenal cortex has differentiated into three distinct zones, these being from the capsule inward: the zona glomerulosa, the zona fasciculata and the zona reticularis. The zona reticularis is adjacent to the medulla. The entire cortex varies in thickness from 0.25 to 1.25 mm. The capsule sends small connective tissue septums into the cortex, which serves as a framework.

The cells of the zona glomerulosa are described by Piersol as being polyhedral and arranged in rounded masses of tortuous groups of cells. Cells of the zona fasciculata are parallel—a radially arranged group of cells. The zona reticularis is narrower than the other zones, and it is formed by the union of the inner ends of the columns of the zona fasciculata. Cells of the zona reticularis have been described by Piersol [16] as being from 15 to 20 microns in diameter. The cytoplasm contains variable amounts of fat granules, which are especially abundant in the zona fasciculata, there being few or none in the zona reticularis. This is such a noticeable finding in the zona fasciculata that the term "spongiocytes" has been applied to cells of this zone.

The adrenal cortex has the richest blood supply of any organ of the body, from 6 to 7 cc. of blood per minute per gram of tissue passing through it.[17] The source of this blood is from the right and left adrenal arteries, which arise directly from the aorta and anastomose freely within the gland. The capillaries are large and sinusoidal and pass into veins which join into a central vein at the hilus. The venous walls of the cortex vary in thickness and in some places are but one or

15. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, Ann. Surg. **100**:670-688 (Oct.) 1934.

16. Piersol, G. A.: Normal Histology, ed. 12, Philadelphia, J. B. Lippincott Company, 1920.

17. Maximow, A. A., and Bloom, William: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 704.

two cells thick. The adrenal gland is innervated chiefly by the splanchnic nerves, these fibers penetrating the capsule with the connective tissue fibers and infiltrating the cortex.

PATHOLOGIC ADRENAL CORTEX

Ewing [18] has arbitrarily classified tumors of the adrenal cortex into: (1) hyperplasia, nodular or diffuse; (2) adenoma, and (3) carcinoma.

Various grades of hyperplasia can be observed. Virchow [19] called this condition "struma suprarenalis;" he made no attempt to differentiate the nodular and the diffuse type. The nodular type is usually well encapsulated, and frequently many areas of hyperplasia can be found in one gland. The diffuse type has recently been more commonly associated with the picture of hirsutism.[15] The cells in diffuse hyperplasia resemble those of the zona glomerulosa; rarely do they simulate those of the zona fasciculata, although the cells in any zone may in part be duplicated. Nodular hyperplasia may be associated with nodules in the liver, and sexual overdevelopment may be seen in this type of condition.

Ewing stated that true adenoma can be distinguished from hyperplasia by its atypical and neoplastic structure. According to him, this is borne out in the so-called adenoma malignum, which is a carcinoma in a previously benign adenoma, and is of rather frequent occurrence. I have studied one such case. Adenoma of the adrenal gland usually occurs singly, but there may be multiple and bilateral growths. The tumor frequently projects from the capsule as a reddish or yellow structure, which is well circumscribed. Hemorrhage and central softening may occur. Some adenomas weigh as much as 4 ounces (114 Gm.) and still retain the characteristics of a benign adenoma. On occasions the adenoma is invaded by fibrous tissue, to the extent that it becomes quite firm and, as a result, is called a "fibro-adenoma." There is a tendency toward hyperchromatism of the nuclei in the true adenoma.

The occurrence of carcinoma of the adrenal gland is not so surprising when one considers the mesothelial origin of the cortex. It is this type of tumor that frequently produces secondary sexual changes.[20] The cells of such a carcinoma may resemble those of any of the layers of the cortex, although most frequently the cells of the zona fasciculata

18. Ewing, James: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 770.

19. Virchow, cited by Wolley, P. G., and Adami, J. G.: A Primary Carcinomatoid Tumor (Mesothelioma) of the Adrenals, with Sarcomatous Metastases, Tr. A. Am. Physicians **17**:627-643, 1902.

20. Keyser, L. D., and Walters, Waltman: Carcinoma of the Suprarenal Associated with Unusual Endocrine Manifestations, J. A. M. A. **82**:87-88 (Jan. 12) 1924.

are simulated. Metastasis is very common, the usual sites being the lungs, liver, adjacent peritoneal lymph nodes and more distant organs. The carcinoma has a tendency to grow rapidly because of its rich blood supply, and the degenerative changes within it are quite common, especially hemorrhage and necrosis.

The carcinoma may attain enormous proportions, Cabot [21] having reported a case wherein the tumor was found to weigh 6 pounds (2,722 Gm.). Hirsutism accompanied the symptoms at the onset.

Because of the large size and early incorporation into the adjacent kidney, much discussion has arisen as to the origin of such a tumor, whether renal or adrenal. Glynn,[22] in an exhaustive study of the adrenal cortex, tended to disagree with those who felt that the renal hypernephroma was primary in adrenal rests. He gave his reasons as being (1) that there was a dissimilarity in the microscopic structure of the two, (2) that the renal hypernephroma apparently never influences growth or sexual characteristics and (3) that it was difficult to explain why adrenal rests, although rather rare in the kidney, should produce such a common tumor as the hypernephroma, which is by far the most common renal tumor, whereas adrenal rests in other organs, which are common, especially in early life, should produce a tumor so infrequently.

The metastatic involvement produced by carcinoma of the adrenal cortex differs from that produced by the so-called renal hypernephroma in that in the case of the former bone is rarely involved, whereas in the case of the latter such involvement is frequent. Lescher and Robb-Smith [23] reported a case of tumor of the adrenal cortex associated with hirsutism in which the entire gland was destroyed. The tumor weighed 593 Gm. and was covered with a thin, yellowish capsule. Holmes [24] described a tumor weighing 1,025 Gm.; subsequent cure of the preexisting hirsutism followed its removal. Glynn examined the specimen and reported a similarity between its cells and those of the zona reticularis. He stated that the cells measured from 20 to 25 microns in diameter and their nuclei from 8 to 9 microns in diameter as compared to 15 microns for the entire cell and 7 microns for the nuclei of normal adult cells fixed in a solution of formaldehyde.

21. Cabot Case Records of the Massachusetts General Hospital, New England J. Med. **208**:546-552 (March 9) 1933.

22. Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumours: Its Relation to Other Ductless Glands, and Especially to Sex, Quart. J. Med. **5**:157-192 (Jan.) 1912.

23. Lescher, F. G., and Robb-Smith, A. H. T.: History of a Case of Carcinoma of the Cortex with Cushing's Syndrome, Proc. Roy. Soc. Med. **27**:404-408 (Feb.) 1934.

24. Holmes, Gordon: A Case of Virilism Associated with Suprarenal Tumour: Recovery After Its Removal, Quart. J. Med. **18**:143-152 (Jan.) 1925.

RESULTS OF STUDY

The average areas of the nuclei and nucleoli were calculated from actual measurements of the nuclei and nucleoli of 20 individual cells in each specimen.

In normal adrenal tissue the areas of the nuclei of cells in the zona glomerulosa varied from 10.09 to 54.51 square microns, whereas the areas of the nucleoli varied from 0.545 to 2.417 square microns. The average area of the former was 30.79 square microns, and that of the latter was 1.297 square microns.

As a result of a study of the zona fasciculata of ten histologically normal adrenal cortices, the nuclei were found to vary in size from 18.17 to 34.32 square microns, and the nucleoli, from 0.545 to 1.27 square microns. The average area of the former was 25.17 square microns, and that of the latter was 0.871 square micron.

As a result of a study of the zona reticularis of ten histologically normal cortices, the nuclei were found to vary in size from 36.35 to 56.54 square microns, and the nucleoli, from 1.26 to 2.52 square microns. The average area of the former was 43.57 square microns, and that of the latter was 1.78 square microns.

In specimens of tissue from a series of growths diagnosed as adenoma of the adrenal cortex and from an adrenal cortex with hemorrhagic inflammation, the smallest average area of the nuclei was 29.61 square microns, and the largest average area of the nuclei was 50.97 square microns. The smallest average area of the nucleoli was 1.17 square microns, and the largest average area of the nucleoli was 3.22 square microns. The actual areas of the nuclei varied from 20.15 to 90.67 square microns, whereas the actual areas of the nucleoli varied from 0.755 to 6.09 square microns. It will be seen that the average area of the nuclei is 37.87 square microns, and that of the nucleoli is 1.95 square microns.

In tissue from growths diagnosed as carcinoma the nuclei ranged in area from 34.21 to 218.10 square microns. The nucleoli varied in area from 1.46 to 65.43 square microns. The average area of the nuclei was found to be 82.18 square microns, and that of the nucleoli was 8.50 square microns.

Considering the group of normal or benign cells in contrast to the group of carcinoma or malignant cells, it is evident that both the nuclei and the nucleoli of malignant cells are larger than those of benign cells. Examination of the results obtained by measuring the size of the nuclei and nucleoli of benign and of malignant cells of the adrenal cortex shows that although both the nuclei and the nucleoli of malignant cells are larger than those of benign cells, the nucleolus of the malignant cell is relatively much enlarged.

With the average measurements of the nuclei and nucleoli of cells of the normal adrenal cortex as 49.76 and 1.97 square microns, respectively, the ratio of the size of the nuclei to that of the nucleoli is found to be 25.2:1; with the average measurements of the nuclei and nucleoli of adrenal adenoma cells as 37.87 and 1.58 square microns, respectively, the ratio is found to be 23.9:1; with the average measurements of the nuclei and nucleoli of cells of the adrenal cortex with hemorrhagic inflammation as 32.04 and 1.51 square microns, respectively, the ratio is found to be 21.2:1, and with the average measurements of the nuclei and nucleoli of adrenal carcinoma cells as 82.14 and 8.50 square microns, respectively, the ratio is found to be 9.67:1. Thus, there is seen to be a characteristic relationship between the size of the nuclei and the nucleoli of benign and malignant cells.

In the histogram showing the sizes of the nuclei (fig. 1) it will be seen that approximately 85 per cent of the nuclei of benign cells fall

Average Measurements of Nuclei and Nucleoli in Various Types of Adrenal Tissue

Adrenal Tissue	Average, Area, Square Microns		Ratio of Nuclei to Nucleoli
	Nuclei	Nucleoli	
Normal adrenal tissue (cortex)	49.76	1.97	25.2:1
Adenomatous tissue	37.87	1.58	23.9:1
Tissue with hemorrhagic inflammation	32.04	1.51	21.2:1
Carcinomatous tissue	82.14	8.50	9.67:1

within the areas of from 30 to 60 square microns; all measure greater than 10 square microns, and the average area is 49.76 square microns. Approximately 85 per cent of the nuclei of malignant cells fall within the measurements of from 40 to 140 square microns, the average area being 82.14 square microns. All measure greater than 30 square microns. Furthermore, 90 per cent of the nuclei of adenoma cells fall within the measurements of from 20 to 50 square microns, the average area being 37.87 square microns. All measure more than 20 square microns. Thus, it is seen that the average size of the nuclei of benign and of malignant cells differ, although there is some overlapping in size when the nuclei of malignant and of benign cells are not differentiated.

In the histogram presenting the sizes of the nucleoli (fig. 2) it will be seen that 100 per cent fall within the areas of from 0.5 to 2.5 square microns, the average size being 1.97 square microns. The nucleoli of adenoma cells vary from 0.5 to 6 square microns, and approximately 85 per cent fall between 1 and 2.5 square microns. Of the nucleoli of carcinoma cells, 68 per cent fall within the range of 2 and 15 square microns, 45 per cent being between 5 and 15 square microns. The average size of these nucleoli is 8.5 square microns. Thus it is seen that when one

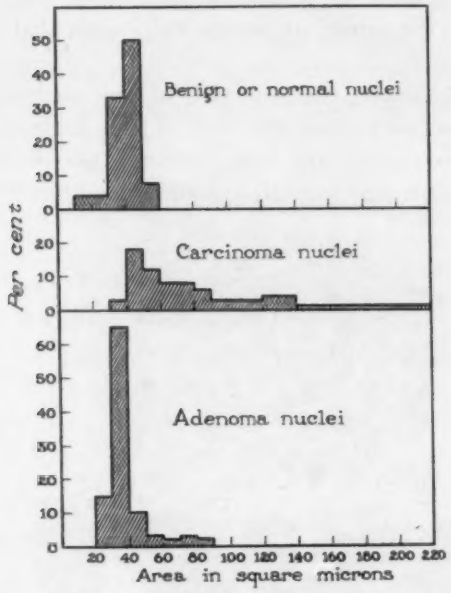

Fig. 1.—Chart showing the percentage distribution and area of nuclei.

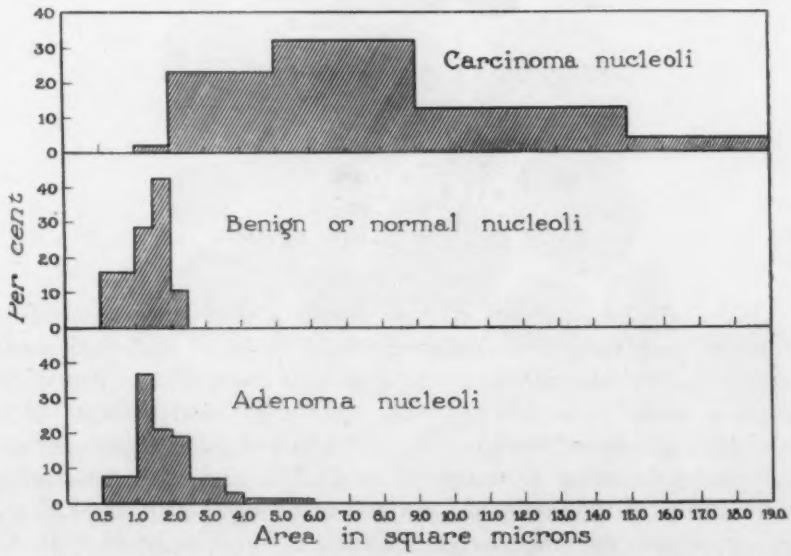

Fig. 2.—Chart showing the percentage distribution and area of nucleoli.

compares the size of the nucleoli of benign cells with that of the nucleoli of malignant cells, there is much less overlapping than when one compares the size of the nuclei of benign cells with that of the nuclei of malignant cells.

It appears, therefore, that the size of the nucleoli is a far better criterion of malignancy than the size of the nuclei and whereas the nuclei of malignant cells are larger than those of benign cells, the nucleoli of malignant cells are relatively enlarged much more than those

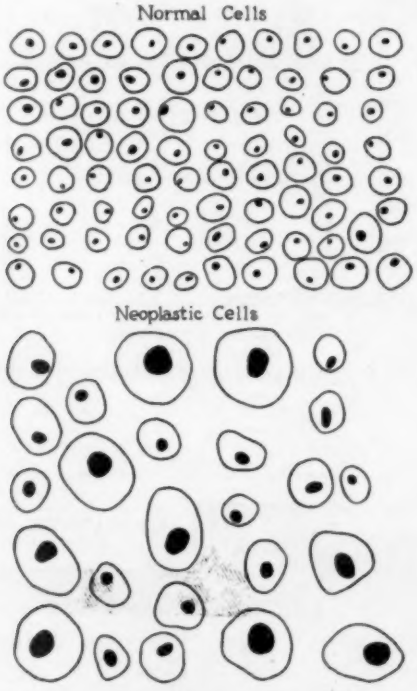

Fig. 3.—Normal and neoplastic cells.

of benign cells (figs. 3 and 4). With the average measurements of the nuclei and nucleoli of malignant cells as 82.14 and 8.05 square microns, respectively, the ratio of the size of the nuclei to that of the nucleoli is found to be 9.67 : 1; with the average measurements of the nuclei and nucleoli of benign cells as 49.76 and 1.97 square microns, respectively, the ratio is found to be 25.2 : 1, and with the average measurements of the nuclei and nucleoli of adenoma cells as 37.87 and 1.58 square microns, respectively, the ratio is found to be 23.9 : 1. On examining these data it can be seen, therefore, that there is a characteristic relationship between the size of the nuclei and nucleoli of benign and malignant cells of the adrenal cortex.

SUMMARY

Twenty cells in each specimen of tissue from four adrenal carcinomas, four adenomas and one adrenal gland with hemorrhagic inflammation and from ten specimens of normal adrenal tissue were studied with particular reference to the size of the nucleus and nucleolus of each cell.

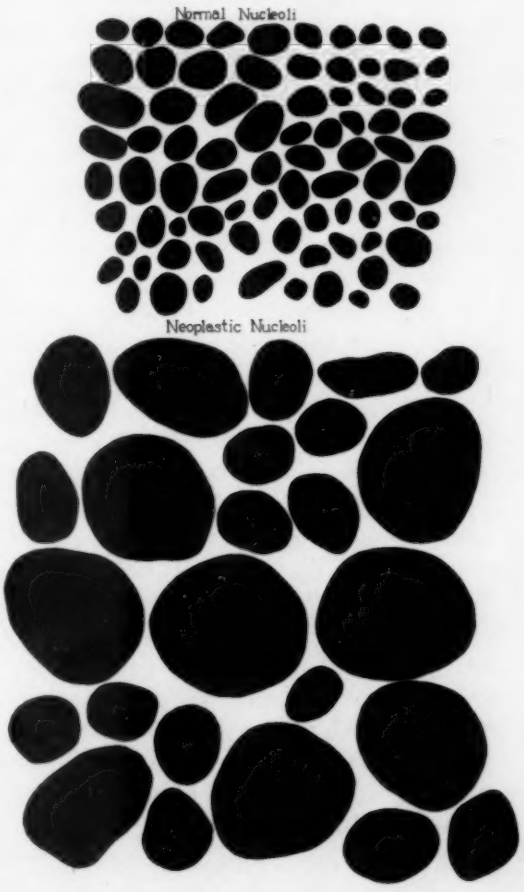

Fig. 4.—Normal and neoplastic nucleoli.

In malignant tissue the average area of the nuclei was 82.14 square microns; in adenomatous tissue it was 37.87 square microns, and in normal adrenal tissue it was 49.76 square microns.

In malignant tissue the average area of the nucleoli was 8.50 square microns; in adenomatous tissue it was 1.58 square microns, and in normal adrenal tissue it was 1.97 square microns.

The ratio of the size of the nuclei to that of the nucleoli in malignant cells was 9.67 : 1 ; in adenoma cells, 23.9 : 1, and in normal adrenal cells, 25.2 : 1.

CONCLUSIONS

The nuclei and nucleoli of malignant cells are larger than those of benign cells. The ratio between the size of the nuclei and the size of the nucleoli in malignant cells is much smaller than that which exists between the size of the nuclei and the size of the nucleoli of benign cells.

MYELOMA AND ITS NEURAL COMPLICATIONS

CHARLES DAVISON, M.D.
AND
BEN H. BALSER, M.D.
NEW YORK

The most frequent neural complications of the myeloma are those referable to the spinal cord and roots. The almost constant involvement of the spinal vertebrae in this disorder readily explains the neural manifestations. The pressure exerted by the invading neoplasm on the spinal cord or by the diseased vertebrae on the vessels of the spinal cord leads to a myelopathic process, thus interfering with the normal conduction of neural impulses of the various fiber tracts. The occurrence of root pains, herpes zoster or peripheral neuritis is the end-result of direct pressure on the roots of the spinal cord, the spinal ganglions and the peripheral nerves. Although metastases to the bones of the skull are frequent, mental symptoms and other signs of cerebral involvement are rarely observed. Compression of the cerebral structures by the metastases to the skull, apparently, is not sufficient to elicit neurologic symptoms.

The rarity of the disease is evidenced by its presence only 3 times in 4,000 autopsies at the Bellevue Hospital (Symmers and Vance [1]) and in 4 instances in 9,000 autopsies at the Johns Hopkins Hospital. In a series of 20,000 patients admitted to the Montefiore Hospital, 12 had myeloma. Of this group, 6,500 came to autopsy, and myeloma was found in 9 instances. The brain and spinal cord were examined in 6 of these cases. Neurologic signs and symptoms secondary to cranial or vertebral involvement were noted in all 12 cases.

This presentation is of interest because of the large number of cases, the direct metastasis to the spinal dura in 1, the involvement of the peripheral nerves in another and the presence of a psychosis in a third instance. Metastasis to the spinal dura and involvement of the peripheral nerves, as far as we know, have not been described in the literature.

REPORT OF CASES

Neural Complications with Cranial or Vertebral Involvement and Removal of the Brain and Spinal Cord.—CASE 1.—D. B., a man aged 52, was admitted to the

From the Neuropathological Laboratory and the Neurological Division, the Montefiore Hospital.

1. Symmers, D., and Vance, D.: The Multiple Myelomata and Their Ability to Metastasize, Ann. Surg. **67**:687, 1918.

Montefiore Hospital on Aug. 20, 1931, with a history of constant pain in the mid-thoracic region for several months, followed by girdle pains and transitory sharp, shooting pains in the lower extremities. In August 1931 there appeared numbness and weakness of both lower extremities followed by complete paraplegia. At about the same time he suffered from constipation, difficulty in starting the urinary stream and reduction in libido. The past history was unimportant, except for the contraction of a chancre in 1900, for which he received antisyphilitic treatment.

Examination.—The blood pressure was 145 systolic and 105 diastolic. A small kyphus was noted at the fourth dorsal vertebra. There was paraplegia with total loss of power in the lower extremities. The deep reflexes of the lower extremities were exaggerated, and there was a Babinski toe sign bilaterally. All forms of sensation were diminished below the fifth dorsal segment.

Laboratory Data.—The urine contained a slight trace of albumin with occasional granular casts. The Bence-Jones protein was not determined. The spinal fluid contained 30 polymorphonuclear leukocytes and 10 lymphocytes and gave a positive reaction to the Pandy test. Manometric studies revealed no evidence of block. Roentgen examination of the spine showed collapse of the ninth dorsal vertebra (fig. 1). The examination of the blood, including chemical studies, gave negative results.

Course.—During the patient's entire stay in the hospital he received large doses of morphine for relief from the intractable pain. On August 25 he became comatose, the blood pressure dropped to 110 systolic and 70 diastolic, a paralytic ileus developed and he died on August 26.

Clinical Diagnosis.—The diagnosis was myeloma of the dorsal vertebrae with compression of the cord.

Autopsy.—Gross Examination: The bodies of the seventh to the ninth dorsal vertebrae were infiltrated by tumor tissue; the ninth dorsal vertebra was fractured (fig. 1). The spinal cord at this level was adherent to the posterior part of the fractured vertebra. The anterolateral surface of the spinal dura was markedly thickened between the sixth and the ninth dorsal segment, and the posterolateral surface was slightly thickened.

Microscopic Examination: Sections of the cord at various levels were embedded in pyroxylin, cut and stained by the myelin sheath, cresyl violet and hematoxylin and eosin methods. In the sections stained by the myelin sheath method, the anterior surface of the spinal dura at the sixth dorsal segment was extensively thickened and was invaded by neoplastic tissue (fig. 2). The fiber tracks appeared to be intact. Under higher power magnification, however, demyelinization of several areas in the anterior columns of the cord was observed. The ventral and dorsal spinocerebellar pathways had a slight honey-combed appearance. There was also demyelinization of the ventral surface of the posterior column of the eighth dorsal segment. The axis cylinders at this level, except for those of the lateral corticospinal tract which were swollen, showed no changes. The anterior and posterior spinal vessels were slightly compressed. The right lateral spinal artery was slightly thickened, and its lumen was constricted. The anterior horn cells disclosed slight retrograde changes, and their Nissl substance stained poorly. Sections above and below the compression did not show any evidence of ascending or descending degeneration.

The tumor consisted of numerous plasma cells and a few giant cells with little stroma (fig. 3). In some areas inflammatory cells, essentially polymorphonuclear leukocytes, were scattered between the plasma cells. The loosely packed plasma

cells were round, oval and polygonal, with homogeneous, pale neutrophilic cytoplasm. Some had a single nucleus, while others were multinucleated. Zones of necrosis were observed, and a few small spicules of bone were found.

Comment.—The patient had root pains for months prior to admission to the hospital. Later there suddenly developed symptoms and signs of a lesion at the level of the fifth and sixth dorsal segments. The neurologic symptoms were the result of compression of the cord by the metastatic myeloma to the spinal dura at that level and not by the fractured dorsal vertebra. It is somewhat difficult to explain the slight impairment of the circulation of the vessels of the spinal cord with

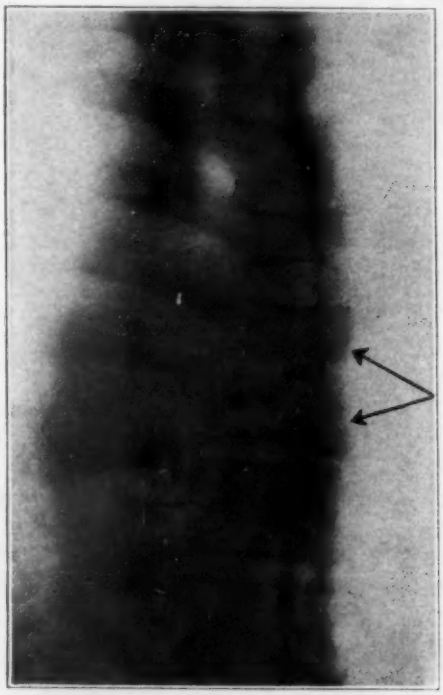

Fig. 1 (case 1).—Roentgenogram showing collapse of the eighth and ninth dorsal vertebrae.

such marked invasion of the dura. The early death of the patient after the sudden paraplegia most likely prevented severe impairment of the circulation of the spinal cord and the production of a marked myelopathic process.

CASE 2.—M. S., a married man aged 43, was admitted to the Montefiore Hospital on Jan. 24, 1931, with a history of shooting pains in the right thoracic region radiating down the right lower extremity since June 1929. The pain became progressively worse, and the patient was subjected to laminectomy in October 1930. After this there gradually developed weakness in both lower extremities and inability to walk.

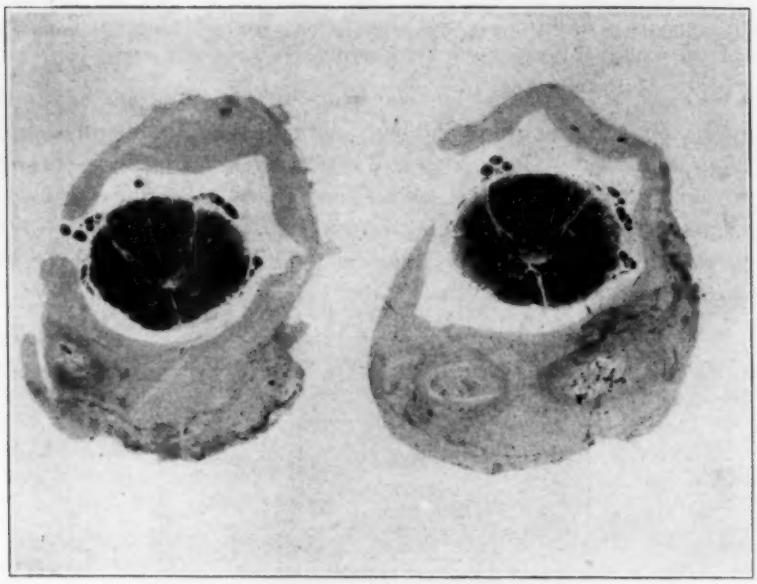

Fig. 2 (case 1).—Sections of the spinal cord showing myelomatous invasion of the thickened ventral spinal dura and mild demyelinization of the lateral tracts. Myelin sheath stain.

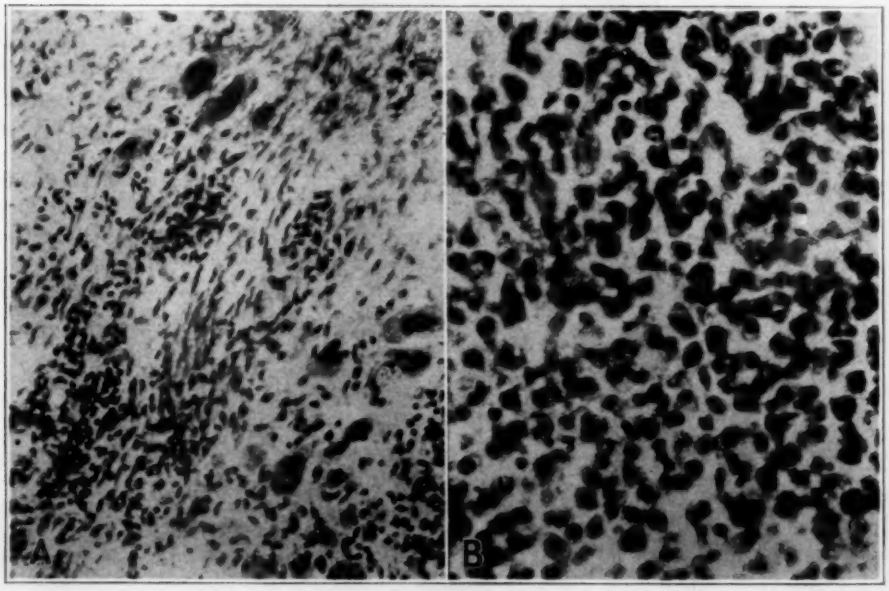

Fig. 3 (case 1).—*A*, section of the myeloma showing giant cells. Cresyl violet stain; × 150. *B*, section of the tumor showing plasma cells. Cresyl violet stain; × 300.

Examination.—The results of the general physical examination were negative. Neurologic examination revealed a flaccid paraplegia, loss of power in the lower extremities, generalized hyperreflexia, a Babinski toe sign bilaterally and allied responses. Percussion and pressure on the dorsal and lumbar vertebrae produced severe pain. There was a belt of hyperalgesia and hyperthermesthesia at the eleventh and twelfth dorsal dermatomes, with diminution of all forms of sensation below that level. The patient had slight difficulty in starting the urinary stream.

Laboratory Data.—Examination of the blood revealed a moderate secondary anemia. On repeated examinations the urine showed heavy traces of albumin. The presence of Bence-Jones bodies was not determined. The Wassermann reac-

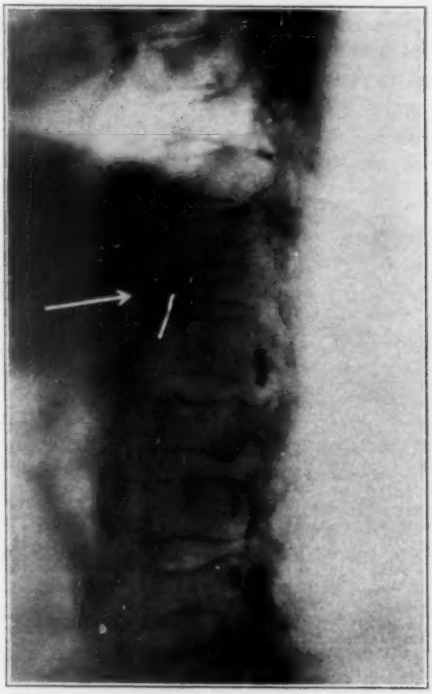

Fig. 4 (case 2).—Roentgenogram showing collapse and destruction of the twelfth dorsal vertebra.

tion of the blood and spinal fluid was negative. The response to the gum mastic test was 0244443200. Manometric studies revealed no evidence of block. Roentgen examination of the vertebral column disclosed collapse of the twelfth dorsal vertebra (fig. 4).

Course.—Shortly after the patient's admission lobar pneumonia developed, from which he recovered. Roentgen examination on May 20 disclosed destruction of several of the thoracic vertebrae with partial collapse of the bodies of the third, fourth and fifth thoracic vertebrae. He received high voltage roentgen therapy to the vertebrae, with some relief from pain. Bronchopneumonia developed, and the patient died on August 28.

Clinical Diagnosis.—The diagnosis was myeloma of the dorsal vertebrae with compression of the cord.

Autopsy.—Gross Examination: The posterior part of the body of the twelfth dorsal vertebra was carious and spongy and replaced by islands of necrotic tissue. The spinal dura at this level was slightly thickened and compressed by the vertebra. The cord was cut transversely, and no abnormalities were encountered. There were no metastases to the other organs.

Microscopic Examination: Sections from various regions of the cord were embedded, cut and stained by the myelin sheath and cresyl violet methods. There was demyelinization of the posterior columns of the third lumbar segment and less demyelinization of the lateral columns and posterior roots (fig. 5). This demyelinization was also present to a slight degree in the lower thoracic and upper lumbar regions. The lateral surface of the dura of the third lumbar segment was thickened (fig. 5) and invaded by bony tissue. The lateral spinal arteries were slightly thickened, had narrow lumens and were compressed by the thickened dura.

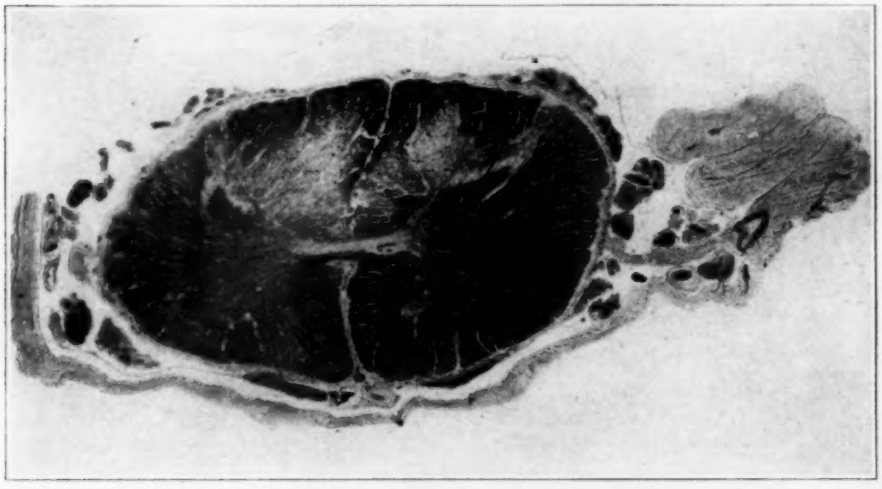

Fig. 5 (case 2).—Section of the spinal cord showing the thickened dura with bony invasion on its lateral aspect and degeneration of the spinal tracts, most marked in the posterior columns. Myelin sheath stain.

Under higher power magnification the posterior columns showed varying degrees of destruction of the myelin sheaths. The anterior horn cells were well preserved except for an occasional ganglion cell in the lower dorsal and upper lumbar regions, which was poorly stained. Segments above this level showed an ascending degeneration of the posterior columns.

The vertebral tumor consisted of loosely and closely packed round, polygonal and oval cells with a homogeneous bluish cytoplasm. The nuclei were large, round and very dark. Most of them were eccentrically placed. Some of the cells were slightly compressed and spindle shaped. Many multinucleated giant cells were seen. The cells were embedded in a hyaline matrix, in which there was also an occasional fat globule.

Comment.—The myeloma found at the twelfth dorsal vertebra and the thickened dura compressed the vessels of the spinal cord at that

level. The neurologic picture was that of a level lesion with motor and sensory disturbances due to vascular obstruction. The excruciating pains produced by pressure on the posterior roots were relieved by high voltage roentgen therapy. Of interest was the lack of improvement in the symptoms after the laminectomy.

CASE 3.—O. B., a married man aged 68, was admitted to the Montefiore Hospital on Oct. 30, 1926. In 1922 he had an attack of lumbago. One year later he experienced severe pain in the lumbar region and pain and a sensation of coldness in the lower extremities. In February 1926 he had urinary retention necessitating catheterization. On admission he was unable to sit or walk because of intense pain across the back and in the lower extremities.

Examination.—There was cardiac enlargement to the left with a mitral systolic murmur. The blood pressure was 130 systolic and 65 diastolic. There was a palpable tender pulsating mass in the middle of the left lumbar region. Neurologic examination disclosed weakness of the left lower extremity, diminished knee and ankle jerks, absence of the right lower abdominal reflex and loss of all forms of sensation below the twelfth dorsal dermatome.

Laboratory Data.—Roentgen examination of the dorsal region of the spine disclosed atrophy of the bone. There were partial destruction and forward dislocation of the second and fourth lumbar vertebrae and complete destruction of the third lumbar vertebra; these vertebrae were surrounded by a mass. There was also a pathologic fracture of the right clavicle. The urine contained heavy traces of albumin, occasional white and red blood cells and hyaline and granular casts. Tests for Bence-Jones protein were negative on several occasions. The blood and spinal fluid were normal.

Course.—Hypostatic bronchopneumonia developed, and the patient died on Jan. 14, 1927.

Clinical Diagnosis.—The diagnosis was vertebral myeloma compressing the spinal cord and cauda equina and metastases to the clavicle and ribs.

Autopsy.—Gross Examination: There was a large encapsulated soft fluctuating vascular mass in the region of the left second to the fifth lumbar vertebrae, which extended 4 cm. to the left of the spinal column posteriorly and from 1 to 2 cm. to the right. The tumor did not extend anteriorly beyond the ligaments of the surfaces of the vertebrae; posteriorly it reached to the spinous processes on both sides. Longitudinal sections through the third and fourth lumbar vertebrae revealed a large vascular and necrotic tumor and small scattered tumor nodules almost entirely replacing the vertebral bodies and spinous processes. The spinal canal was narrowed by the tumor, and the cord and cauda equina at this level were compressed. The dura and cord were not invaded by the neoplasm. The right clavicle and the sixth left rib were invaded by tumor nodules.

Microscopic Examination: Except for a narrowing of the lumens of the spinal vessels and destruction of occasional myelin fibers of various tracts, the spinal cord appeared to be normal.

The tumor was highly vascular and consisted of compact polygonal cells with small round nuclei and uniformly relatively pale staining cytoplasm; the stroma was scanty. There were innumerable cells which closely resembled the plasma cell type of myelocyte.

Comment.—The neurologic signs and symptoms in this case were essentially due to the compression of the lumbar region of the spinal cord and its vessels and the cauda equina. The radicular pains were the most outstanding feature. The spinal dura and cord, in contrast to those in cases 1 and 2, were not invaded by the tumor.

CASE 4.—H. S., a man aged 46, entered the Montefiore Hospital on Nov. 26, 1930, with a history of slight pain in the right ribs for fourteen years. Seven years later removal of part of the fourth right rib led to a diagnosis of myeloma. In November 1929 the patient experienced severe pain in the left ribs, back, thighs and legs. There was slight improvement in the symptoms after high voltage roentgen therapy. In June 1930 he complained of headaches.

Examination.—On the patient's admission to the hospital there were observed a slight limitation of the motion of the head and neck and tenderness on percussion over the cervical and lumbar regions of the spine. There was a slight secondary anemia. The roentgenograms showed scattered areas of osseous destruction in the skull and in both scapulas and both femurs. The patient received high voltage roentgen therapy and was discharged in March 1931 as slightly improved.

On readmission to the hospital on April 25, 1931, he complained of headache, pain in the neck and chest and inability to straighten out his back.

Laboratory Data.—Roentgen examination revealed almost complete destruction of the body of the first lumbar vertebra. There was severe anemia, as indicated by 1,900,000 red cells, 5,200 white cells and a hemoglobin content of 30 per cent. The total serum protein, which was 7.65 Gm. per hundred cubic centimeters (albumin, 4.04 Gm.; globulin, 3.61 Gm.), decreased to 3.61 Gm. (albumin, 2.53 Gm.; globulin, 1.08 Gm.). The urine showed albumin, Bence-Jones protein and many granular casts. The Congo red test was positive for amyloidosis on Feb. 4, 1932.

Course.—The patient was put on a high caloric, high protein, high salt diet with unlimited fluids, and within two weeks the serum protein content rose to 4.73 Gm. (albumin, 3.22 Gm.; globulin, 1.51 Gm.). At no time was the patient edematous. Dorsal and sacral decubitus ulceration developed, followed by a rise in temperature to 102.4 F. On February 22 the patient became very weak and was unable to stand, sit or turn from side to side, with complete loss of power in all extremities. Neurologic examination at this time disclosed diminished reflexes of the upper extremities, hyperactive knee jerks and absence of the left ankle jerk and of the abdominal and cremasteric reflexes. Bronchopneumonia developed, and death occurred on February 24.

Clinical Diagnosis.—The diagnosis was vertebral myeloma, with compression of the cord, and myelomas of the skull, clavicle and ribs.

Autopsy.—Gross Examination: The essential lesions were found in the skeletal system. The calvarium was thin and transparent. Its inner table and, in places, its outer table were studded with circumscribed peculiar grayish red to grayish brown areas. The base of the skull was similarly involved. Several ribs were fractured, and on sectioning the cut surface showed either pale fat marrow or a few localized glistening grayish yellow gelatinous areas. The bodies of the eighth and ninth dorsal, sacral and some of the coccygeal vertebrae were fractured, and the fragments were dislocated. These vertebrae were destroyed, and were replaced by hemorrhagic and peculiar grayish red gelatinous masses. The spinal cord was not removed.

Microscopic Examination: The tumor consisted of small and large lymphocytes and plasma cells, irregular large homogeneous acidophilic globules, foreign body giant cells and numerous bone spicules and osteoclasts.

Examination of the brain did not disclose any pathologic changes..

Comment.—Despite the extensive involvement of the skull, the brain remained unaffected. The headaches were undoubtedly caused by the metastases to the skull. The changes in the spinal cord could not be detected as the spinal cord was not removed at autopsy. The weakness, the inability to move the extremities and the hyperactive knee jerks and the absence of superficial reflexes noticed toward the end of the illness were most likely due to a mild myelopathic process resulting from compression of the vessels of the spinal cord. This case is of special interest because of the duration of the illness for sixteen years. Although the diagnosis was not made until seven years after the initial symptom of pain in the right rib, the presence of the tumor nodule in the same area strongly suggests the existence of the myeloma over the sixteen year period. This is the first instance of a myeloma in which the patient lived sixteen years.

Case 5.—A. S., a woman aged 58, was admitted to the Montefiore Hospital on March 15, 1931, complaining of weakness, loss of weight and backache since December 1930. The pains were aggravated on motion and were relieved by rest in bed.

Examination.—Stiffness of the thoracic and lumbar regions of the spine with marked limitation of motion was noted. There was tenderness over the fifth, sixth and seventh ribs on the right side and over the mid-dorsal region of the spine. The base of the left lung below the angle of the scapula was dull on percussion. Breathing over this area was almost bronchial in type. A few nodules were palpated in the left breast.

Laboratory Data.—Roentgen examination disclosed areas of bony destruction scattered throughout all the vertebrae with narrowing of the bodies of the eleventh and twelfth dorsal vertebrae. There were also areas of bony destruction scattered throughout all the ribs, the shoulder girdle, the humeri, the right lower jaw, the pelvic bones and the upper end of the shaft and the trochanter of the right femur. All the bones of the skull were completely riddled with metastases, varying in size from that of a pinhead to that of an almond (fig. 6). The urine was positive for albumin and Bence-Jones protein. Examination of the blood revealed 3,080,000 red cells, 3,500 white cells, 55 per cent hemoglobin, 50 per cent polymorphonuclear leukocytes and 44 per cent transitionals with moderate anisocytosis, poikilocytosis and achromasia. Toward the end of the illness examination of the blood disclosed 1,800,000 red cells, 4,200 white cells, 54 per cent polymorphonuclear leukocytes, 18 per cent small lymphocytes, 20 per cent large lymphocytes and 5 per cent monocytes. There was central pallor of the red cells, with poikilocytosis, anisocytosis and polychromophilia.

Course.—On July 16 herpes zoster developed over the entire dorsum and left side of the trunk. On June 1, 1933, the patient had delusions that the nurse was putting poison in her food. A careful mental examination revealed a well adjusted syntonic person with no previous handicaps or manifestations. She reiterated the

persecutory delusion for several weeks, during which time she refused to have anything to do with that nurse. Then she gradually changed her mind and began to take the medication from the same nurse. Later she accused another nurse of poisoning her and had ideas with reference toward other people. Throughout the examination she did not smile or laugh despite attempted provocations. Whenever she saw any one laugh, she thought that they were laughing at her. Her insight was poor. She explained that the poison had not taken effect because "her husband brought her some castor oil" and because she refused "to take medication from the nurse who had evil designs" on her. She was fairly well oriented. Later she also had auditory and visual hallucinations.

The patient received high voltage roentgen therapy without much improvement. Toward the end marked secondary anemia and bronchopneumonia developed, and death occurred on July 5, 1934.

Clinical Diagnosis.—The diagnosis was multiple myelomas with metastases to the skull and dura, compression of the cerebral hemispheres and psychosis.

Fig. 6 (case 5).—Roentgenogram of the skull showing multiple areas of osseous destruction.

Autopsy.—Gross Examination: Myelomatous nodules were found throughout the skeletal system, as disclosed at the roentgen examination. All the cranial bones were riddled with metastases. The brain was markedly anemic. There was slight dilatation of the ventricles. Myelomatous masses were not found in the brain. The spinal cord was anemic.

Microscopic Examination: The cerebral dura was invaded by numerous myelomatous nodules (fig. 7). Sections of the cortex disclosed a washed-out appearance of the ganglion cells and ischemic cell changes. Most of these nerve cells showed chronic cell changes. The giant pyramidal cells of Betz presented marked chromatolytic changes with the nuclei displaced to the periphery (fig. 8).

The spinal cord showed no abnormality.

The tumor was a typical plasma cell myeloma without giant cells.

Comment.—The outstanding features in this case were the metastatic nodules in the skull and cerebral dura, a psychosis with paranoid

trends and herpes zoster. Whether the psychosis was due to the secondary anemia or to compression of the cerebral structures by the myeloma is difficult to state. Similar mental pictures have been observed in some cases of pernicious anemia. It should be emphasized that the psychosis preceded the severe secondary anemia by one year and that psychoses were not found in any of the other cases of myeloma with marked secondary anemia. The metastatic myeloma to the skull in this case

Fig. 7 (case 5).—Section of the cerebral dura showing invasion by myelomatous nodules. Hematoxylin and eosin stain; × 50.

was more extensive than in the other cases in our series. The metastases to the cerebral dura and skull possibly caused compression and constriction of the cerebral vessels, which led to ischemia and changes in the nerve cells.

Case 6.—R. B., a woman aged 49, was admitted to the Montefiore Hospital on May 29, 1935, with a history of an anemia since 1932 and occasional mild pains

in the arms since January 1933. This was soon followed by a tingling sensation in the finger-tips and excruciating pains in the arms, fingers and hands. In June 1934 she experienced numbness and weakness of both hands. Prior to admission to this hospital, examination at the Mount Sinai Hospital revealed secondary anemia, mild peripheral neuritis of the upper extremities and a low grade fever, the temperature ranging from 100 to 102 F. The blood count disclosed a hemoglobin content of from 48 to 62 per cent, without any leukocytosis but some increase in monocytes.

Examination.—Physical examination disclosed pallor, a systolic murmur over the precordium, with its greatest intensity over the aortic area, and palpable lymph

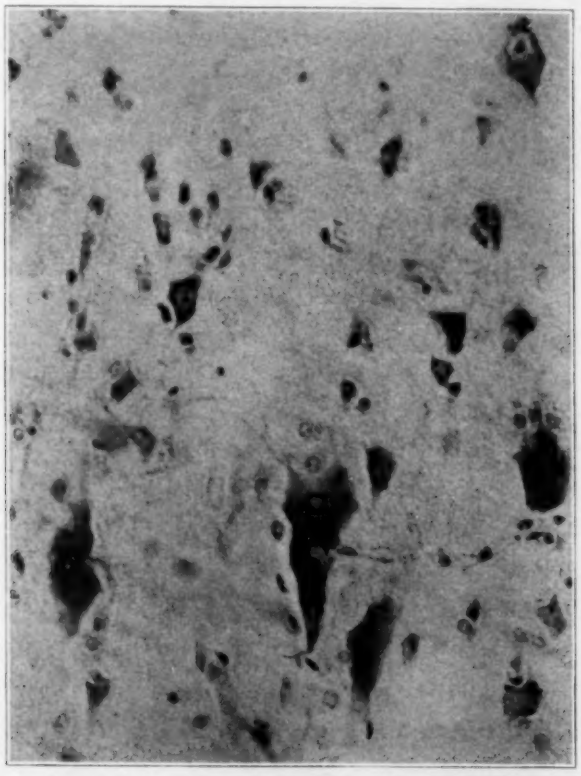

Fig. 8 (case 5).—Section of the cortex showing chromatolysis, vacuolation and degeneration of the giant pyramidal cells of Betz. Cresyl violet stain; × 200.

nodes in both axillae. Neurologic examination revealed bilateral atrophy of the thenar and hypothenar eminences and interossei muscles without fibrillations. There were diminished vibratory sensation in the toes and a smooth and atrophic tongue with marked tremor. The knee jerks were diminished but present. Position sense was retained.

Laboratory Data.—The urine was positive for albumin but negative for Bence-Jones protein. Examination of the blood disclosed 2,800,000 red cells, 50 per cent hemoglobin and 9,800 white cells, with microcytosis, poikilocytosis and central pallor. The Wassermann reaction of the spinal fluid was negative. The reaction

to the gum mastic test was 0000000000; the total protein content was 31.3 mg. per hundred cubic centimeters. Analysis of the gastric contents showed the presence of free hydrochloric acid. Roentgen examination disclosed absorption of bone in the outer third of the right clavicle, cloudiness of both antrums and a small circumscribed nodule in the lower lobe of the right lung.

Course.—The general weakness became progressively worse, and roentgen examination of the right elbow showed a destructive lesion of the lower end of the humerus. On August 2 the patient sustained a right supracondylar pathologic fracture. Soon after she became delirious, dyspneic and cyanotic and died on the same day.

Clinical Diagnosis.—The diagnosis was multiple myeloma and compression of the brachial plexus.

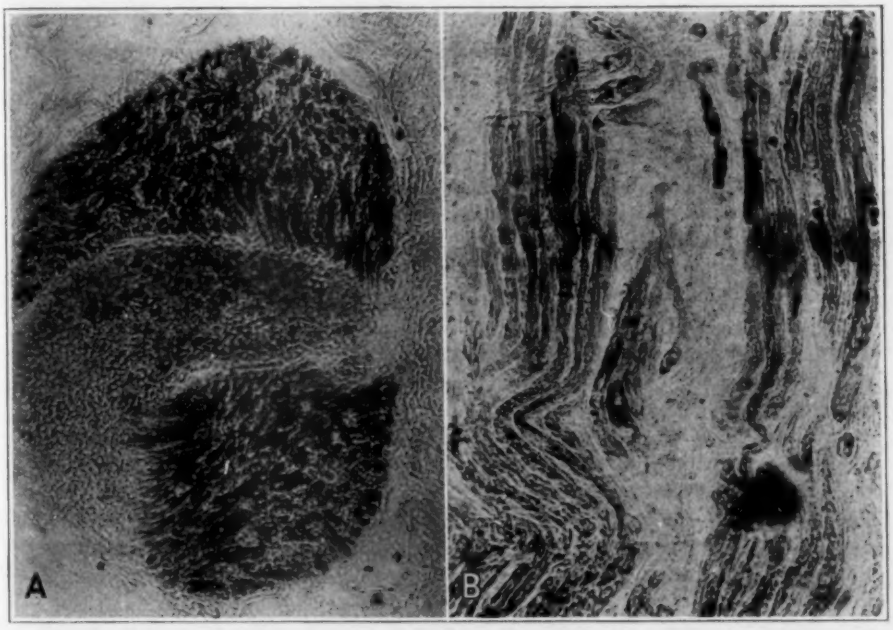

Fig. 9 (case 6).—*A*, section of the spinal cord showing partial destruction of the posterior root. Myelin sheath stain; × 128. *B*, section of the spinal cord showing disintegration of myelin in the nerve fibers of the brachial plexus. Sudan III stain; × 116.

Autopsy.—Gross Examination: The brain and spinal cord showed no gross abnormalities. The brachial plexus was removed, and sections were embedded.

Microscopic Examination: In sections through the medulla oblongata in the region of the twelfth nerve nucleus, a few of the nerve cells of the left hypoglossal nucleus were diminished in number and size and showed slight chromatolysis.

A section of the spinal cord, the eleventh dorsal segment, showed partial demyelinization of one of the posterior roots (fig. 9 *A*). In the preparation stained with cresyl violet the anterior horn cells in the cervical region of the spinal cord stained poorly. In the lower cervical region an occasional pyknotic anterior horn cell was noted.

There were occasional demyelinization of single fibers and breaking-down and disintegration of myelin within the nerves of both brachial plexuses (fig. 9 *B*). In the preparation stained with sudan III there were slight deposits of fat (fig. 9 *B*), while in the preparation stained by the Bielschowsky method the axis cylinders were slightly swollen and disintegrated.

Comment.—The diminution and slight pathologic changes within the nerve cells of the left hypoglossal nucleus were most likely due to the compression of the hypoglossal nerves with retrograde degeneration within its respective nerve cells. The other changes, such as bilateral atrophy of the thenar and hypothenar eminences and the diminished vibratory sense in the toes, were possibly caused by compression of the peripheral nerves and the roots. In the absence of myelomatous invasion of the peripheral nerves, the peripheral neuritis might have been secondary to the severe anemia or to some unknown toxic factors.

Neural Complications with Vertebral and Cranial Involvement.[2]—CASE 7.—H. S., a man aged 71, was admitted to the Montefiore Hospital on Aug. 11, 1929, with a history of having received a blow over the chest six months before. The next day he experienced excruciating pain in the lower part of the spine and the lower extremities and was confined to bed for several weeks. Later he also complained of pain in the right shoulder and the left side of the chest. The pains were somewhat relieved when he was lying down.

Examination.—There was a soft mass over the right clavicle near the sternal border. The expansion of the chest was poor. There was an area of bronchial breathing over the base of the right lung posteriorly and an area of diminished breathing with a few râles over the lower left side of the chest anteriorly. A systolic murmur was heard over the apex. The liver was about two fingerbreadths below the costal margin. There were tenderness over the lower vertebrae and kyphosis of the dorsal portion and part of the lumbar portion of the spine. The knee jerks were present and equal, but there was ankle clonus bilaterally without any pathologic reflexes. On August 17 the patient became markedly dyspneic and died on the same day.

Laboratory Data.—Roentgen examination showed numerous areas of destruction of the cranial bones. Areas of rarefaction were also seen in the ribs, lumbar vertebrae and pelvis. There were pathologic fractures of the ribs. Examination of the blood revealed 1,720,000 red cells, 7,800 white cells and 30 per cent hemoglobin. The urine was positive for albumin but negative for Bence-Jones protein.

Clinical Diagnosis.—The diagnosis was multiple myeloma.

Autopsy.—Gross Examination: Numerous myelomatous masses were found in the bony structures, as revealed at the roentgen examination. The portions of the body of the lower lumbar vertebrae and of the left innominate bone showed an extensive replacement of marrow by tumor tissue. The brain and spinal cord were not removed.

Microscopic Examination: The diagnosis on the basis of the microscopic picture was myeloma.

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2. Autopsy was performed in some of these cases, but the brains and cords were not removed.

Comment.—Although the lumbar vertebrae and the skull were riddled with myelomatous masses, the neurologic signs, except for ankle clonus bilaterally, were negative. Apparently, the compression of the vessels of the spinal cord by the tumor was insufficient to have caused a myelopathic process. The excruciating pains in the lower extremities were undoubtedly due to compression of the roots by the vertebral metastases. High voltage roentgen therapy was not administered, as the patient died shortly after his admission to the hospital.

CASE 8.—L. S., a woman aged 58, was admitted to the Montefiore Hospital on Oct. 6, 1931, with a history of pain in the left shoulder since 1924. Six years later there appeared a lump in the upper left side of the chest. The patient experienced pains in the upper and lower extremities, which were aggravated by any motion and were somewhat relieved when sitting down.

Examination.—A bulging above the clavicle and a movable mass, 8 cm. in diameter, over the left supraclavicular space were found on examination. Another firm immovable mass, 8 cm. in diameter, was seen over the inner third of the left clavicle. The lungs were clear and resonant, and the breathing was vesicular. There was a systolic murmur over the apex. The left arm could be raised only to a horizontal position, and there was limitation of rotation.

Laboratory Data.—Roentgen examination disclosed pathologic fracture of the left humerus, a large mass in the superior mediastinum, pathologic fracture of the neck of the left femur, areas of osseous destruction in the right innominate bone and in the shafts of the left tibia and fibula, extensive destruction and collapse of the body of the eleventh dorsal vertebra and partial destruction of the right half of the body of the tenth dorsal vertebra (fig. 10). Circumscribed areas of osseous destruction varying in size from that of a pinhead to about 1.5 cm. in diameter were noted in several ribs and in the skull. The urine was negative for albumin and Bence-Jones protein. Blood examination revealed 3,100,000 red cells, 4,800 white cells, 60 per cent hemoglobin, 65 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 2 per cent eosinophils, 1 per cent monocytes and 2 per cent transitionals.

Course.—The patient received high voltage roentgen therapy over these regions and was discharged somewhat improved on November 4. She was readmitted to the hospital on Jan. 12, 1933, with pains in the lumbosacral region and in the lower extremities. On September 21 after an enema, the patient complained of a "break" in the back and girdle pains, with immediate loss of power in the lower extremities. Neurologic examination at this time disclosed marked tenderness over the tenth dorsal to the second lumbar vertebrae and a lesion at the level of the tenth dorsal segment, with complete flaccid paraplegia, absence of knee and ankle jerks, loss of all forms of sensation and retention of urine and feces. The patient died of bronchopneumonia on September 28. Autopsy was not performed.

Clinical Diagnosis.—The diagnosis was vertebral myeloma, with compression of the spinal cord and multiple myelomas.

Comment.—In this case there were destruction of the eleventh dorsal vertebra and collapse of its body with sudden compression of the spinal cord and its vessels, leading to neurologic signs and symptoms of a level lesion. The metastasis to the skull did not give rise to mental symptoms or neurologic signs.

Case 9.—H. D., a man aged 30, was admitted to the Montefiore Hospital on Feb. 25, 1930, with a history of pain in the left shoulder and in the chest since August 1929. After a spinal tap on January 17 he experienced complete loss of sensation below the nipples, stiffness and inability to move the legs, incontinence of urine and loss in sexual power. Laminectomy was done on January 20, between the second and the seventh dorsal segment. An extradural tumor was removed, which on histologic examination proved to be a myeloma. After laminectomy there was some return in sensation and in the motor power of the lower extrem-

Fig. 10 (case 8).—Roentgenogram showing extensive destruction and collapse of the body of the eleventh dorsal vertebra and partial destrucrion of the body of the tenth dorsal vertebra.

ities. In October 1930 there was a recurrence of the girdle pains. The administration of high voltage roentgen therapy resulted in diminution of the pain and some return in sexual power.

Examination.—Physical examination revealed a limited expansion of the wall of the chest with all the sounds normal. Neurologic examination disclosed marked diminution in the motor power of the lower extremities, an increase in the deep reflexes, ankle clonus bilaterally, absence of abdominal and cremasteric reflexes and a positive Babinski toe sign and allied reflexes bilaterally. Pain, temperature and touch sense were impaired below the seventh dorsal segment; hypesthesia was less

marked in the sacral region, vibration was lost from the knees down and position sense was impaired in the knees and ankles and lost in the toes. There were also spontaneous flexion movements in one or the other limb, but never both, when the patient lay in bed quietly. There was diminution in libido and urinary retention.

Laboratory Data.—During the first admission roentgen examination of the dorsal region of the spine disclosed evidences of a laminectomy extending from the fourth to the tenth dorsal vertebrae, with partial collapse of the body of the sixth dorsal vertebra. There were also small circumscribed areas of osseous absorption in the left parietal region. The manometric readings disclosed a partial subarachnoid block with a positive globulin reaction and a total protein content of 25.3 mg. Examination of the blood revealed 75 per cent hemoglobin, 3,510,000 red cells, 8,600 white cells, 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. The urine was negative for albumin and Bence-Jones protein.

Course.—The patient received further high voltage roentgen therapy, after which there was some return in sensation below the seventh dorsal segment. The spinothalamic sensory disturbances had disappeared, but the changes in the posterior column were still present. The patient was able to walk without assistance, although the gait remained spastic. The spontaneous flexion movements had also disappeard. The deep reflexes, however, remained unchanged. The patient was discharged as improved on December 26. He was again readmitted to the hospital on March 11, 1931, bcause of a pathologic fracture of the left arm. The neurologic condition remained unchanged. There was, in addition, herpes zoster over the right side of the thigh and of the abdomen, which cleared up under high voltage roentgen therapy. The patient became progressively worse and died of bronchopneumonia on July 24, 1931. Autopsy was not performed.

Clinical Diagnosis.—The diagnosis was multiple myeloma, with compression of the spinal cord.

Comment.—This case is of significance because of the sudden onset of a lesion at the level of the seventh dorsal segment after a spinal tap. In contrast to the second case, laminectomy and removal of the myeloma followed by high voltage roentgen therapy resulted in marked improvement of the neurologic signs.

Case 10.—I. K., a man aged 60, was admitted to the Montefiore Hospital on Feb. 13, 1929, complaining of pain in the right hip and in the back since 1927. The pain came on in spasms and was most noticeable when the patient moved about but was absent when he was lying still. About five months later he was unable to stand because of weakness in the lower extremities. In January 1929 he complained of pain in the region of the sixth to the eighth dorsal vertebrae.

Examination.—Physical examination revealed a prominence between the eighth and the twelfth thoracic vertebra, marked tenderness in this region and limitation of motion. There was an area of dulness, with diminished breath sounds over the lower level of the left scapula. The liver was palpable 2 cm. below the costal margin. Neurologic examination revealed pain over the lumbosacral region. All the deep reflexes were hyperactive but equal. A questionable hypalgesia was found in the third, fourth and fifth right sacral dermatomes. There were herpetic eruptions from the second lumbar to the fifth sacral segments on the right.

Laboratory Data.—Roentgen examination disclosed destruction and partial collapse of the body of the eleventh dorsal vertebra (fig. 11). There were a few small areas of osseous absorption in the parietal, occipital and temporal regions of the skull. The red cell count ranged between 3,500,000 and 2,100,000; the hemoglobin content, from 70 to 40 per cent; the white cell count, from 4,800 to 2,600, with 28 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes and 24 per cent myelocytes. The urine was positive for albumin and Bence-Jones protein.

Course.—The patient received high voltage roentgen therapy, with slight improvement in the symptoms. Later the axillary glands became enlarged. Death occurred on May 15. Autopsy was not performed.

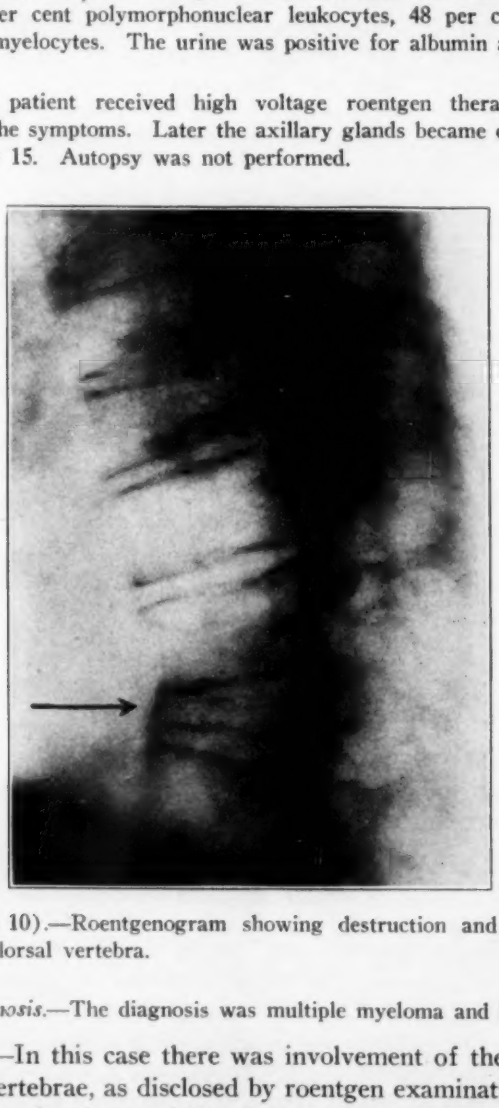

Fig. 11 (case 10).—Roentgenogram showing destruction and partial collapse of the eleventh dorsal vertebra.

Clinical Diagnosis.—The diagnosis was multiple myeloma and herpes zoster.

Comment.—In this case there was involvement of the skull and the lower dorsal vertebrae, as disclosed by roentgen examination. The neurologic signs consisted essentially of root pains and herpes zoster along the distribution of the second to the fifth sacral roots.

Case 11.—H. A., a man aged 43, was admitted to the Montefiore Hospital on March 19, 1929, with a history of excruciating pains in the left lower anterior part of the chest radiating to the regions of the scapula, back and neck since October 1928. The pains would be relieved when he was sitting or lying quietly.

Examination.—Physical examination disclosed tenderness on pressure of the anterior part of the chest at the level of the sixth and seventh ribs. There was a soft systolic murmur at the apex. The neurologic examination, except for a generalized hyperreflexia, gave negative results.

Laboratory Data.—Roentgen examination disclosed multiple areas of osseous absorption scattered throughout all the bones of the skull, the seventh left rib and in both ilia; a partial collapse of the bodies of the seventh, eighth and twelfth dorsal vertebrae, and sclerosis of the bone in the lower lumbar vertebrae. Examination of the blood showed 2,560,000 red cells and 6,400 white cells, with 48 per cent hemoglobin, 62 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, 8 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The urine contained granular casts and white blood cells and was positive for albumin and Bence-Jones protein.

Course.—The patient became weaker, until he was hardly able to walk. He complained of constant throbbing headaches and sticking sensations over the upper left and right sides of the chest anteriorly, the lower extremities and the left arm. A small amount of high voltage roentgen therapy was administered, but owing to the critical condition of the patient it had to be discontinued. Twitching movements and uremic manifestations developed, with death on May 12.

Clinical Diagnosis.—The diagnosis was multiple myeloma.

Autopsy.—Gross Examination: Some of the ribs were thickened and infiltrated by metastases. Sections through the lower part of the spine and other bones showed irregularly grayish discoloration in the medullary tissue. The brain and spinal cord were not removed.

Microscopic Examination: The growth proved to be a myeloma.

Comment.—The inability to walk, the hyperreflexia, the sticking sensations over the chest, the twitching movements and the throbbing headaches were undoubtedly caused by the myeloma compressing the brain, spinal cord and roots. The localization of nodules within the skull and vertebrae, as shown by roentgen examination, confirms this opinion, although the brain and spinal cord were not removed at autopsy.

CASE 12.—G. C., a woman aged 55, was admitted to the Montefiore Hospital on Oct. 12, 1928, complaining of weakness in the lower extremities, inability to walk and pains in the left arm, shoulders, hips and thighs since January 1928.

Examination.—There was extreme tenderness of the long bones on the left side and of the left ribs on movement or pressure. There was dulness on percussion of the chest, and râles were heard at the base posteriorly. A loud high pitched systolic murmur was audible over the precordium. The neurologic examination disclosed only absence of knee jerks.

Laboratory Data.—Roentgen examination disclosed bony destruction of the fourth, sixth, seventh and eighth ribs on the right side and of the seventh and eleventh ribs on the left side. The left shoulder and humerus contained large circumscribed areas of osseous destruction with a pathologic fracture through the lower third of the humerus. Similar areas of destruction were noted in the pelvic bones, the trochanters and the upper end of the shafts of both femurs. Numerous small circumscribed areas of osseous destruction of varying size were noted in all bones of the skull. Examination of the blood revealed 3,340,000 red cells, 50 per cent hemoglobin, 9,800 white cells, 55 per cent polymorphonu-

clear leukocytes, 37 per cent lymphocytes and 4 per cent myelocytes, with anisocytosis, poikilocytosis and two normoblasts. The urine was positive for albumin and Bence-Jones protein.

Course.—The patient received high voltage roentgen therapy, with some improvement. Later tumor masses were noted in the right parietal and in the right temporofrontal region. The administration of high voltage roentgen therapy resulted in some relief from pain. However, the patient became progressively worse and died on Nov. 29, 1929. A postmortem examination was not performed.

Clinical Diagnosis.—The diagnosis was multiple myeloma.

Comment.—The neurologic signs, except for the absence of knee jerks, were negative. The inability to walk was most likely due to the numerous tumor nodules in the bones of the lower extremities.

COMMENT

In the first 3 cases in the series there were signs and symptoms of a level lesion. These were caused by compression of the vessels of the spinal cord by the diseased or fractured vertebrae. In the first case there was direct compression of the anterior spinal artery by a metastatic myeloma to the spinal dura. Direct myelomatous implantations in the spinal dura, as far as we know, have not been reported in the literature. In cases 2 and 3, and possibly in case 4, the diseased vertebrae compressed the dura and the vessels of the spinal cord. In both instances, the dura under the influence of the compressing agent, became extensively thickened and in addition to the diseased vertebrae acted as a factor in compressing the spinal cord. As in most of the cases recorded in the literature, the thoracic portion of the spinal cord was the usual site of compression; in the first case the midthoracic region was involved, and in the second and third cases, the lower thoracic region. The lumbar vertebrae were also implicated in cases 3 and 4. Spinal subarachnoid block was not noted in any of these cases. The root pains can easily be explained on the basis of direct compression of the posterior roots. In contrast to the cases recorded by Jacox and Kahn,[3] Klemme[4] and Denker and Brock,[5] and the eighth case in our series, improvement did not occur in our second case after laminectomy. High voltage roentgen therapy, however, gave some relief. Involvement of a single vertebra was not found in any of our cases. Myelomatous invasion of the vertebral column only with destruction of several vertebrae was noted in cases 1 and 2.

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3. Jacox, H. W., and Kahn, E. A.: Multiple Myeloma with Spinal Cord Involvement, Am. J. Roentgenol. **30**:201, 1933.

4. Klemme, R. M.: Plasma-Cell Myelomas Causing Cord Compression: Report of Five Cases, South. M. J. **26**:692, 1933.

5. Denker, P. G., and Brock, S.: The Generalized and Vertebral Forms of Myeloma: Their Cerebral and Spinal Complications, Brain **57**:291, 1934.

In the entire group of cases of neural complications with vertebral involvement, the outstanding clinical findings consisted of localized vertebral tenderness, severe pain which was relieved when the patients were lying down (cases 5, 10 and 11), the presence of compression of the cord (cases 1, 2, 3, 8, 9 and 11), compression of the roots resulting in herpes zoster (cases 5, 9 and 10) and psychosis (case 5). In case 6 the peripheral neuritis of the upper extremities may have been due to compression of the brachial plexus, to the severe secondary anemia or to other unknown toxic factors. Peripheral neuritis in cases of myeloma, as far as is known, was not recorded by other observers. In case 5, in spite of vertebral involvement, signs or symptoms of compression of the cord were absent, and in case 7, although the vertebrae were destroyed, the only neurologic sign elicited was ankle clonus.

The fifth case is of special interest because of the marked psychosis with a paranoid trend. Whether this was caused by the secondary anemia or by the compression of the cerebral structures by the metastatic nodules in the cerebral dura and skull is difficult to state. It is well known that psychoses are observed in cases of pernicious and of severe secondary anemia. The mental symptoms in this case, however, preceded the severe secondary anemia by one year. We are inclined to believe that the psychosis was the expression of an organic lesion due to cerebral circulatory dysfunction, as shown by the ischemic and other pathologic changes of the nerve cells. The circulatory dysfunction was the result of compression of the cerebral vessels by the myelomatous nodules in the cerebral dura and skull. The patients in cases 4 and 11 had headaches, possibly due to the metastatic nodules to the skull and dura. In case 11 the twitching movements were most likely due to cerebral compression. Neurologic signs, such as convulsions and polydipsia, as a result of involvement of the skull, were encountered in the first case reported by Denker and Brock.[5] Aronsohn [6] described diabetes insipidus in a case of multiple myeloma of the bones of the base of the skull.

The group of cases in which the brains and cords were not removed also presented interesting features. In contrast to case 2, the symptoms referable to the spinal cord in case 9 showed marked improvement after laminectomy. The additional administration of high voltage roentgen therapy cleared up almost all of the symptoms. This was the only case in this group in which there was a partial subarachnoid block. In this last group there were 3 cases with slight neural complications (cases 10, 11 and 12), and we wondered whether they were caused by compression of the cord. This is true of such findings as weakness of the lower

6. Aronsohn, H. G.: Zur pathologischen Anatomie und Symptomatologie der multiplen Myelome, Virchows Arch. f. path. Anat. **281**:78, 1931.

extremities in case 10, the generalized hyperreflexia in cases 10 and 11 and the absence of knee jerks in case 12.

The symptoms referable to the spinal cord in cases of myeloma are most likely due to compression of the vessels of the spinal cord by the tumor or fractured vertebrae, leading to a myelopathic process. Direct compression of the spinal cord by the neoplasm, although less frequently observed, is another possibility. Nonne,[7] Kreuzer [8] and others expressed the belief that the neurologic signs are produced by the action of a toxin liberated by the neighboring myeloma. Nonne [7] came to this conclusion because he found the diseased vertebrae slightly lower than the supposedly compressed segments and because microscopic examination did not reveal any demonstrable lesion of the cord. Kreuzer,[8] in 1 case, found multiple areas of degeneration in the dorsolateral tracts of the cord, most marked in the ninth and tenth thoracic segments, although the fourth and fifth thoracic vertebrae were implicated. He therefore concluded that the symptoms referable to the spinal cord were not caused by mechanical pressure but by distant effects of the toxins. If this theory is correct, it is to be expected that in cases of myeloma signs referable to the spinal cord should be encountered more frequently distally instead of at the site of the diseased vertebrae. A survey of our cases and of others recorded in the literature proves, however, the contrary. As shown by Keschner and one of us (Davison),[9] the degree of compression of the spinal vessels by extradural neoplasm or agents varies, depending on the location and size of the compressing agent. The resulting myelopathic process at the level of compression will be slight, moderate or marked, depending on the foregoing factors as well as on the length of time of compression. Our cases of myeloma illustrate this. In the first case, although there was direct metastases to the spinal dura, because of the short duration of the pressure exerted the changes in the spinal cord were insignificant. The so-called influence of liberated toxins on the nervous system from this or other neoplastic diseases is undoubtedly emphasized too much.

It is to be stressed that the vertebral form of the disease occurs most frequently. In contrast to the 3 cases reported by Denker and Brock,[5] in none of our cases was there involvement of a single vertebra.

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7. Nonne, M.: Zur Klinik der Myelomerkrankung der Wirbelsäule, Neurol. Centralbl. **40**:1, 1921.

8. Kreuzer, H.: Plasmazelluläres Myelom mit multipler teilweise haemorrhagischer Herdmyelose der Medulla spinalis, Deutsche Ztschr. f. Nervenh. **90**: 224, 1926.

9. Keschner, M., and Davison, C.: Myelitic and Myelopathic Lesions: V. Compression of the Spinal Cord by Expanding Lesions Producing Mild, Moderate or Marked Interference with the Circulation Leading to Myelopathy, Arch. Neurol. & Psychiat. **30**:592 (Sept.) 1933.

In cases 1 and 2, however, several vertebrae were diseased without other skeletal involvement.

Our material is of interest from other clinical angles. Most of our cases conform to Geschickter and Copeland's [10] dictum of the cardinal symptoms and signs in the diagnosis of multiple myeloma: (*a*) multiple involvement of the skeletal trunk, (*b*) pathologic fractures, (*c*) Bence-Jones proteinuria in from 65 to 70 per cent of the cases, (*d*) characteristic backache with early signs of paraplegia, (*e*) inexplicable anemia and (*f*) chronic nephritis, retention of nitrogen and hypertension. The symptoms and signs referable to vertebral involvement were amply discussed. It would be advisable to comment briefly on the other symptoms and signs.

An interesting feature is the age incidence. In 8 patients the disease appeared in the fifth and sixth decades and in 2 in the seventh and eighth decades (cases 3 and 7). Of unusual interest is the occurrence of the disorder in the patient in case 9 at the age of 29 and in the patient in case 4 at the age of 32. In Geschickter and Copeland's series,[10] 5 patients were under 35 years of age. There were 8 males and 3 females in our series. This is in accordance with the general view that the disease occurs twice as often in males as in females. The duration of the disease in our series varied between six months and sixteen years. It lasted a year or less in cases 1, 2, 3, 5, 7, 11 and 12; two years in cases 9 and 10; three years in case 6; nine years in case 8, and sixteen years in case 4. The duration of the illness over a period of sixteen years is the longest ever recorded in the literature. Slavens [11] reported a usual duration of about two years with a hopeless prognosis. As will be demonstrated, life can be prolonged by the administration of high voltage roentgen rays.

The Bence-Jones protein was positive in 5 of our cases. In the first 2 cases the test was not performed. The percentage of positive Bence-Jones protein in the urine in our cases is slightly lower than that in the case of Geschickter and Copeland,[10] who found it present in 65 per cent of their series, and much lower than in the cases of Magnus-Levy,[12] who found it positive in 80 per cent of his series. The percentage in our series might have been higher had the test been performed in the first 2 cases.

Severe secondary anemia was present in cases 2, 4, 5, 6, 7, 10 and 11 and moderate secondary anemia in cases 8, 9 and 12. Pathologic

10. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931.

11. Slavens, J. J.: Multiple Myeloma in a Child, Am. J. Dis. Child. **47**:821 (April) 1934.

12. Magnus-Levy, A.: Ueber die Myelomkrankheit, Ztschr. f. klin. Med. **121**:533, 1932.

fractures were noted in most of our cases. Nephrosis, frequently reported in this disorder, was found in 10 of our cases.

Seven patients received high voltage roentgen treatment. In 4 there occurred slight improvement (cases 2, 4, 8 and 10), in 2 marked improvement (cases 9 and 11) and in 1 no improvement (case 5). The patients in cases 1, 3, 6, 7 and 12 did not receive deep high voltage roentgen therapy. Of the symptoms, pain was most frequently relieved by this type of therapy. The improvement in our cases after this treatment corresponds to that recorded by others and at present remains the best form of therapy. Jacox and Kahn [3] reported 2 cases in which excellent results followed laminectomy and roentgen therapy, 1 patient doing well five and one-half years after the onset of the symptoms. Wakeley's [13] patient was doing well for four and one-half years, and Coley's [14] patient remained well nine years and was still alive in 1931 after the same form of treatment. The condition in case 2 became worse after laminectomy but showed definite improvement after high voltage roentgen therapy. In the presence of metastases to the spinal cord with signs of compression of the cord, it is advisable to precede the administration of high voltage irradiation by laminectomy.

CONCLUSIONS

Twelve cases of multiple myeloma are reported. In 6 of these in which autopsy was performed, involvement of the spinal cord, roots, peripheral nerves or brain was found. In 6 cases with signs of lesions of the spinal cord or roots, the neural structures were not removed.

In most of the patients with lesions of the spinal cord the neurologic symptoms were produced by compression of the vessels of the spinal cord. A myelopathic process resulted from interference with the circulation. The damage to the fiber tracts depended on the degree and duration of the compression. In case 1 there was a direct metastasis to the spinal dura. Such lesions were, as far as we know, never described before.

The herpes zoster noted in a number of these cases was caused by the direct compression of the spinal roots by the neoplasm. In case 6 the peripheral neuritis may have been due to compression of the brachial plexus, severe anemia or unknown toxic factors.

In case 5 the myelomatous nodules of the cerebral dura and skull resulted in interference with the cerebral circulation and the production of a paranoid psychosis.

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13. Wakeley, C. P. G.: Plasma-Celled Myelomatosis, Proc. Roy. Soc. Med. **25**:150, 1931.

14. Coley, W. B.: Multiple Myeloma, Ann. Surg. **93**:77, 1931.

EXPERIMENTAL PRODUCTION OF GOITER

HOWARD R. MAHORNER, M.D.
NEW ORLEANS

Numerous attempts have been made by various investigators to produce goiter experimentally in animals. In a review of the literature it is striking that there are so many diverse experimental solutions of a problem about which so little is known. In many instances the observer was too anxious to note hyperplasia of the thyroid gland, and possibly because of enthusiasm alone he found it. Moreover, the question of control for such experiments repeatedly arises. Were they adequately controlled? It does not seem sufficient, especially in endemic goiter regions, to have the thyroid gland of a dog examined grossly and microscopically for the first time at the end of the period that a trial stimulus has been applied and to pronounce it hyperplastic by comparing it with a gland from an entirely different dog. Because of the great number of the experimental methods that have been reported as successful in the production of hyperplastic changes in the thyroid gland, it is almost impossible to eliminate all except one possible factor in one type of experiment. However, in any one type of experiment the results must be most carefully compared with the normal and, if possible, with a basic normal in the same animal.

The present report is based on experiments performed in an attempt to produce goiter in dogs and in guinea-pigs. In the experiments on dogs an attempt was made to insure a most rigid control by the following procedure:[1] At a preliminary operation the thyroid gland of each dog was measured, and a small piece, 2 by 2 mm., was removed from one of the lobes, usually the right. Subsequently, observations at operation or at necropsy were made, and a similar specimen was removed which was compared with the section obtained at the preliminary operation. In this manner each dog was self-controlled, although there were other controls from which sections were taken but in which no unusual stimulus was applied.

From the Department of Surgery, Tulane University School of Medicine.

Aided by a grant from the New Orleans Academy of Sciences under its affiliation with the American Association for the Advancement of Science.

1. Mahorner, H. R.: Attempts to Produce Hyperplasia in Thyroid by Destruction of Part of Adrenals and by Infection, Proc. Soc. Exper. Biol. & Med. **29**:1076, 1932; Attempts to Produce Hyperplasia of Thyroid Gland by Infection and by Injury to the Adrenal Gland, ibid. **30**:770, 1933.

It is not desirable or feasible to review in detail all the literature pertaining to attempts to produce artificially hyperactivity or hyperplasia of the thyroid gland, but a few articles are cited to show a basis for some of my experiments.

Halsted [2] (1888) concluded from his microscopic studies of the thyroid glands of dogs suffering from low grade peritonitis induced by the intraperitoneal injection of a culture of staphylococci that infection causes hyperplastic changes in the thyroid gland. Womack and Cole [3] reported microscopic changes considered indicative of hyperplasia in the thyroid glands of dogs after implanting infected foreign bodies in the muscles of the necks of the animals. Plummer and Mayo [4] observed clinical hyperthyroidism in certain instances after the onset of an infectious process and expressed the belief that the infection precipitated the hyperthyroidism. McCarrison,[5] working in India, came to the conclusion that goiter is a filth-borne disease. Among numerous other experimental results, he reported [6] enlargement of the thyroid glands of rats kept under insanitary conditions.

According to Hellwig,[7] the theory that a high calcium intake might be responsible for the production of goiter is over one hundred years old, Waller [8] in 1912 suggested that hard water is the responsible factor in the production of goiter. Hellwig,[7] Hibbard [9] and others reported that a high calcium intake caused an increase in the size of the thyroid glands of animals. Bircher [10] in 1914, in experimental work on rats, found enlargement of the thyroid glands of animals which imbibed water of certain municipalities, whereas this observation was not made in controls

2. Halsted, W. S.: Reconsideration of the Question of Experimental Hypertrophy of the Thyroid Gland and the Effect of Excision of This Organ on Other of the Ductless Glands, Am. J. M. Sc. **147**:56, 1914.

3. Womack, N. A., and Cole, W. H.: Normal and Pathologic Repair in the Thyroid Gland, Arch. Surg. **23**:466 (Sept.) 1931.

4. Plummer, W. A., and Mayo, C. H.: Surgical Operations and Associated Infections as Possible Etiologic Factors in the Development of Exophthalmic Goiter, Surg., Gynec. & Obst. **53**:721, 1931.

5. McCarrison, Robert: The Etiology of Endemic Goiter, Milroy Lectures, London, John Bale, Sons & Danielsson, 1913.

6. McCarrison, Robert: Interaction of Food and Sanitary Condition in Causation of Thyroid Disease, Indian J. M. Resea. :h **20**:957, 1933.

7. Hellwig, C. A.: Morphogeographic and Experimental Studies on Etiology of Goiter, West. J. Surg. **41**:453, 1933.

8. Waller, H. E.: The Relationship of the Thyroid Gland to Other Internal Secretions of Sexual Origin, Practitioner **89**:279, 1912.

9. Hibbard, J. S.: Experimental Thyroid Hyperplasia: Increased Intake of Chloride Combined with Diet Deficient in Iodine as a Factor, Arch. Surg. **26**: 648 (April) 1933.

10. Bircher, E.: Das Kropfproblem, Beitr. z. klin. Chir. **89**:1, 1914.

which were given water from other sources. Webster and Chesney [11] reported the occurrence of goiter in rabbits fed on a diet purely of cabbage.

Golyakowsky [12] in 1899 reported that ligation of the adrenal vessels resulted in elevation of the basal metabolic rate. The metabolic rate was said to decrease slowly after an initial rise within ten days followed by a subsequent elevation to plus 50 per cent between the second and the fourth week. A return of the basal metabolic rate to normal or below occurred in the sixth or seventh week. Marine and Baumann [13] in 1921, using rabbits, obtained a rise in the metabolic rate in 57 per cent of instances in which the adrenal glands were injured or removed. They found that dogs died within twenty-four hours after bilateral adrenalectomy, whereas rabbits were able to survive the procedure, probably because of accessory adrenal tissue in the latter. The increased metabolism continued for one, two or three weeks with or without slight remissions. Marine [14] in 1930 expressed the opinion that this experimental condition is similar to exophthalmic goiter.

The following authors, to cite only some of the many who have written reports on the subject, have presented evidence obtained from experiments on animals, either by measuring the metabolism or by histologic and chemical studies of the thyroid gland and its effect on metamorphosis in tadpoles and salamanders, that extracts from the anterior lobe of the pituitary body activate the thyroid gland, diminish the colloid content of the follicle, diminish the iodine content of the gland and elevate the basal metabolic rate: Smith and Smith,[15] Schwartzbach and Uhlenhuth,[16] Silberberg,[17] Uhlenhuth and Schwartzbach,[18] Loeb and

11. Webster, B., and Chesney, A. M.: Studies in the Etiology of Simple Goiter, Am. J. Path. **6**:275, 1930.

12. Golyakowsky, cited by Marine and Baumann.[13]

13. Marine, D., and Baumann, E. J.: Influence of Glands with Internal Secretion on Respiratory Exchange: Effect of Suprarenal Insufficiency (by Removal or by Freezing) in Rabbits, Am. J. Physiol. **57**:135, 1921.

14. Marine, D.: Studies on Etiology of Goiter Including Graves' Disease, Ann. Int. Med. **4**:423, 1930.

15. Smith, P. E., and Smith, I. P.: The Repair and Activation of the Thyroid in the Hypophysectomized Tadpole by the Parenteral Administration of Fresh Anterior Lobe of the Bovine Hypophysis, J. M. Research **43**:267, 1922.

16. Schwartzbach, S. S., and Uhlenhuth, E.: Anterior Lobe Substance, the Thyroid Stimulator, Proc. Soc. Exper. Biol. & Med. **26**:153, 1928.

17. Silberberg, M.: Effects of Combined Administration of Extracts of Anterior Lobe of Pituitary and Potassium Iodide on Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **27**:166, 1929.

18. Uhlenhuth, E., and Schwartzbach, S. S.: Anterior Lobe, the Thyroid Activator, Anat. Rec. **42**:41, 1929.

Bassett,[19] Aron,[20] Benedict, Putnam and Teel,[21] Siebert and Smith,[22] Janssen and Loeser,[23] Loeser,[24] Loeb and Friedman,[25] Schockaert,[26] Grant,[27] Verzár and Wahl,[28] Siebert and Thurston,[29] Closs, Loeb and MacKay,[30] Junkmann and Schoeller,[31] Thurston,[32] Anderson and Collip,[33] Greep,[34] Collip and Anderson,[35] Friedgood [36] and others.

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19. Loeb, L., and Bassett, R. B.: Effect of Hormone of Anterior Pituitary on Thyroid Gland in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **26**:860, 1929.

20. Aron, M.: Action de la préhypophyse sur le thyroïde chez le cobaye, Compt. rend. Soc. de biol. **102**:682 (Nov. 29) 1929; Particularites histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse, ibid. **103**:145 (Jan. 24) 1930.

21. Benedict, E. B.; Putnam, T. J., and Teel, H. M.: Early Changes Produced in Dogs by Injecting Sterile Active Extract from Anterior Lobe of Hypophysis, Am. J. M. Sc. **179**:489, 1930.

22. Siebert, W. J., and Smith, R. S.: The Effect of Various Anterior Pituitary Preparations upon Basal Metabolism in Partially Thyroidectomized and in Completely Thyroidectomized Guinea Pigs, Am. J. Physiol. **95**:396, 1930.

23. Janssen, S., and Loeser, A.: Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**:517, 1931.

24. Loeser, A.: Hypophysenvorderlappen und Jodgehalt der Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**:530, 1931.

25. Loeb, L., and Friedman, H.: Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, Proc. Soc. Exper. Biol. & Med. **29**:172, 1931.

26. Schockaert, J. A.: Hyperplasia of Thyroid and Exophthalmos from Treatment with Anterior Pituitary in Young Duck, Proc. Soc. Exper. Biol. & Med. **29**:306, 1931.

27. Grant, M. P.: The Release of Follicular Colloid from the Thyroid of Necturus Maculosus Following Heteroplastic Anterior-Pituitary Implants, Anat. Rec. **46**:373, 1930.

28. Verzár, F., and Wahl, W.: Wirkung der Hypophysenvorderlappen-hormons auf den O_2-Verbrauch von Meerschweinchen, Biochem. Ztschr. **240**:37, 1931.

29. Siebert, W. J., and Thurston, E. W.: Basal Metabolism After Potassium Iodide with Acid Extract of Anterior Pituitary Glands, Pituitary Tablets and with Thyroid, Proc. Soc. Exper. Biol. & Med. **29**:652, 1932.

30. Closs, K.; Loeb, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland, J. Biol. Chem. **96**:585, 1932.

31. Junkmann, K., and Schoeller, W.: Ueber das thyreotrope Hormon des Hypophysenvorderlappens, Klin. Wchnschr. **11**:1176 (July 9) 1932.

32. Thurston, E. W.: A Comparison of Hypertrophic Changes in Thyroid Caused in Different Species by Acid Extract of the Anterior Lobe of the Bovine Pituitary Gland, Arch. Path. **15**:67 (Jan.) 1933.

33. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **30**:680, 1933.

34. Greep, R.: Effect of Luteinizing and Follicular Stimulating Fractions of Pituitary on Thyroid, Proc. Soc. Exper. Biol. & Med. **30**:1362, 1933.

(Footnotes continued on next page)

The literature on the subject contains numerous reports of changes in the thyroid gland produced by other substances.[36a] Even the foregoing literature contains many conflicting reports. It could easily be shown that the substances which are said to be efficacious in producing changes in the thyroid gland are numerous and that the results reported by different authors are frequently so incongruous that doubt is cast on the reliability of both, and the weight of whichever one is correct is miscarried.

INFECTION AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Fourteen dogs were used in an attempt to produce hyperplasia of the thyroid gland by means of infection. No attempt was made to produce a deficiency of iodine in the diet in this or in the other experiments. The fourteen dogs were divided into three groups, the first two consisting of four dogs each and the last of six dogs (table 1). At a preliminary operation the thyroid gland of each dog was exposed by a midline incision. The gland was measured, and a piece of tissue approximately 2 by 2 mm. was removed from the anterior border of the right lobe. This was sectioned and stained with hematoxylin and eosin for comparison as a microscopic control with subsequent sections. At the time of the first operation a contaminated foreign body was sewed into the right sternocleidomastoid muscle of the dog. A different contaminating culture was used in each group. In the first group (dogs 20, 21, 22 and 23) the foreign body was a small coil of silver wire contaminated with a pure culture of staphylococci. Each of these wounds remained infected throughout the experiment, and at the end of four, eight, sixteen and twenty-five days, respectively, the dogs were killed. The thyroid glands were measured again, and each was sectioned and stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog. In no instance was there any definite change in the thyroid gland, either grossly or microscopically.

The experiment on the second group of dogs (53, 54, 55 and 56) was conducted in the same manner as that on the first group, except that the foreign body was a small piece of tape, approximately 0.5 by 0.5 cm., which was contaminated with a mixed culture of excrement obtained during colostomy on a human being. The dogs were killed after eight, seventeen, thirty-two and sixty-four days, respectively. The wound of the first three showed infection at the time the animal was killed. In the last dog the wound was healed. There were no appreciable gross or microscopic changes in any of the thyroid glands when the specimens obtained at necropsy were compared with those obtained at the preliminary operation.

There were six dogs (58, 59, 60, 61, 62 and 63) in the third group. The foreign body was tape contaminated with mixed anaerobic and aerobic cultures

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35. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**:76 (Jan. 13) 1934.

36. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea-Pigs: Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**:48, 1934.

36a. For a more detailed review see Mahorner, H. R.: Recent Advances in Surgery of the Thyroid Gland, Surgery **2**:280 (Aug.) 1937.

of excrement obtained at colostomy on a human being. The contaminated tape was sewed into the right sternocleidomastoid muscle at the preliminary operation, at which time the lobes of the thyroid gland were measured and a biopsy specimen was taken from the right lobe. The dogs were killed by electrocution at the end of nine, twenty, twenty-one, thirty and fifty days, respectively, and at the time

TABLE 1.—*Results of Implantation of Infected Foreign Bodies*

Dog No.	Initial Weight, Kg.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
20	8.7	Implantation of silver wire contaminated with staphylococci into muscle of the neck	4	Infected wound	Hyperplasia (?)
21	9.1	Implantation of silver wire contaminated with staphylococci into muscle of the neck	8	Infected wound	No change
22	7.5	Implantation of silver wire contaminated with staphylococci into muscle of the neck	16	Infected wound	No change
23	7.7	Implantation of silver wire contaminated with staphylococci into muscle of the neck	25	Infected wound	No change
53	8.18	Implantation of tape contaminated with mixed culture into muscle of the neck	8	Infected wound	No change
54	11.7	Implantation of tape contaminated with mixed culture into muscle of the neck	17	Infected wound	No change
55	...	Implantation of tape contaminated with mixed culture into muscle of the neck	32	Infected wound	No change
56	...	Implantation of tape contaminated with mixed culture into muscle of the neck	64	Normal; wound healed	No change
59	9.8	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	9	Infected wound; culture showed mixed infection, bacilli and cocci	No change
62	9.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	20	Infected wound; culture showed mixed infection	No change
63	6.3	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	20	Infected wound; culture showed mixed infection	Retrogressive change
58	9.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	21	Infected wound; culture showed mixed infection	No change
60	7.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	30	Infected wound; culture showed mixed infection	No change
61	7.0	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	50	Wound healed	No change

each animal was killed the right sternocleidomastoid muscle was explored aseptically and the region of the implanted foreign body located. An abscess was found in all dogs except the last. These abscesses were cultured, and in each instance a mixed culture of organisms was found. At necropsy the size of the thyroid gland was measured. Sections were made of each lobe, and these were stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog. In no instance was there gross or microscopic evidence of change in the thyroid gland.

The results in these experiments support the conclusion that a focus of infection in the dog does not produce changes in the thyroid gland suggestive of hyperplasia, at least within a period of thirty-two days. Whereas these results do not prove definitely that infection is not a factor in the production of goiter, they do not corroborate the observations (that infection does produce hyperplasia of the thyroid gland) of other investigators whose similar experiments were less well controlled.

I have examined the thyroid glands of a number of other dogs (not included in this series) that died of infections and have never found microscopic evidence that the infection induced hyperplasia. It is true that by careful study one can pick out small individual areas in which the acini are small and have less colloid than other areas of the gland. The colloid may even appear slightly bluish, but this is not unmistakable evidence of hyperplasia, because similar areas can be found in sections from the thyroid glands of other normal control animals. Desquamation of cells into the acini was found in tissue which has undergone postmortem degeneration. Selected microscopic fields are not to be accepted as representative of the appearance throughout an entire section. Unmistakable evidence of diffuse histologic changes is presented in certain experiments reported herein by deliberately avoiding the fallacy of judging the appearance of a whole gland from that of one particular field. By care exerted to show widest discrepancies in microscopic fields and not the average appearance of the section, an author can demonstrate variations that suggest that microscopic changes have taken place when this is not actually true (figs. 1 and 2). Enthusiasm and eager credulousness may be responsible for an incorrect interpretation of small selected areas as evidence of hyperactivity of the thyroid gland. What is really desirable in such experiments is changes so striking that the evidence is incontestable.

DISTURBANCE OR DEFICIENCY IN THE ADRENAL GLANDS AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Because of the repeatedly expressed opinions that the cause of hyperthyroidism is dysfunction of the adrenal gland and because of the experiments of Marine and Baumann [13] showing that an increase in the basal metabolic rate resulted from removal of part of the adrenal tissue or from freezing the adrenal glands, I attempted to repeat the experiments, using a different method to note the effect of adrenal "deficiency" on the thyroid gland. A section from the thyroid gland of an animal removed after injury to the adrenal gland, the interval after injury varying in different animals, was compared with a section removed at a preliminary operation. Marine and Baumann [13] stated that after decreasing the amount of adrenal tissue by removal in rabbits or after

freezing the adrenal glands the basal metabolic rate was elevated. Marine [14] concluded from this that the elevation of the basal metabolic rate indicates true hyperthyroidism. Granting that the etiologic factor in hyperthyroidism originates outside the thyroid gland, it is safe to conclude that true hyperthyroidism will be attended by some evidence of hyperplasia in the thyroid gland albeit secondary to a stimulus outside the gland. Conversely, it is fair to assume that absence of hyperplasia under similar conditions in which there is elevation of the basal metabolic rate indicates that the elevated basal metabolic rate is not due to true hyperthyroidism.

Dogs were used for this experiment. At a preliminary operation the thyroid gland was exposed through a midline incision and measured. A piece of tissue,

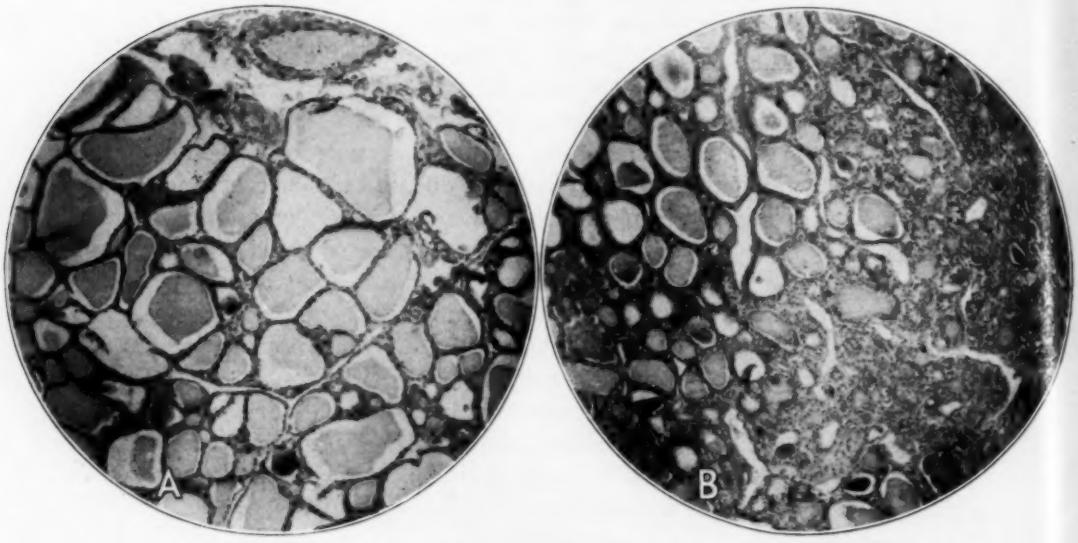

Fig. 1.—*A* and *B* are two different sections taken from the thyroid gland of a dog at the time after the animal had received 1 cc. of the gonadotropic principle of the urine of pregnant women daily for twelve days. There is more colloid and the acini are larger in *A* than in *B*. Tiny vesicles may be seen in the colloid in *B*, and the epithelial cells are more cuboidal, but this section is a selected area. There was no essential difference in the preliminary sections and the twelve day sections. This shows that erroneous results may be demonstrated by selecting foci not representative of the average in a section for photomicrography. The magnification of *A* and *B* is the same.

2 by 2 mm., was removed from the anterior border of the right lobe. The wound was closed, and at a subsequent operation, after the wound had healed, the adrenal glands were exposed either through two lumbar incisions or through a midline abdominal incision. (The former was found to be more satisfactory.) The adrenal glands were crushed with a hemostat, and from one third to one half of one of the glands was left intact. The extent of this procedure is indicated in

table 2. The wound was closed, and the animals either died or were killed in from five to one hundred and twenty-seven days. In the first ten days after the procedure the animals appeared sick, were apathetic and moved slowly, and several of them died. In some of the animals the systolic blood pressure fell from 180 to 80 mm. of mercury. Several of the animals died within the first few days after

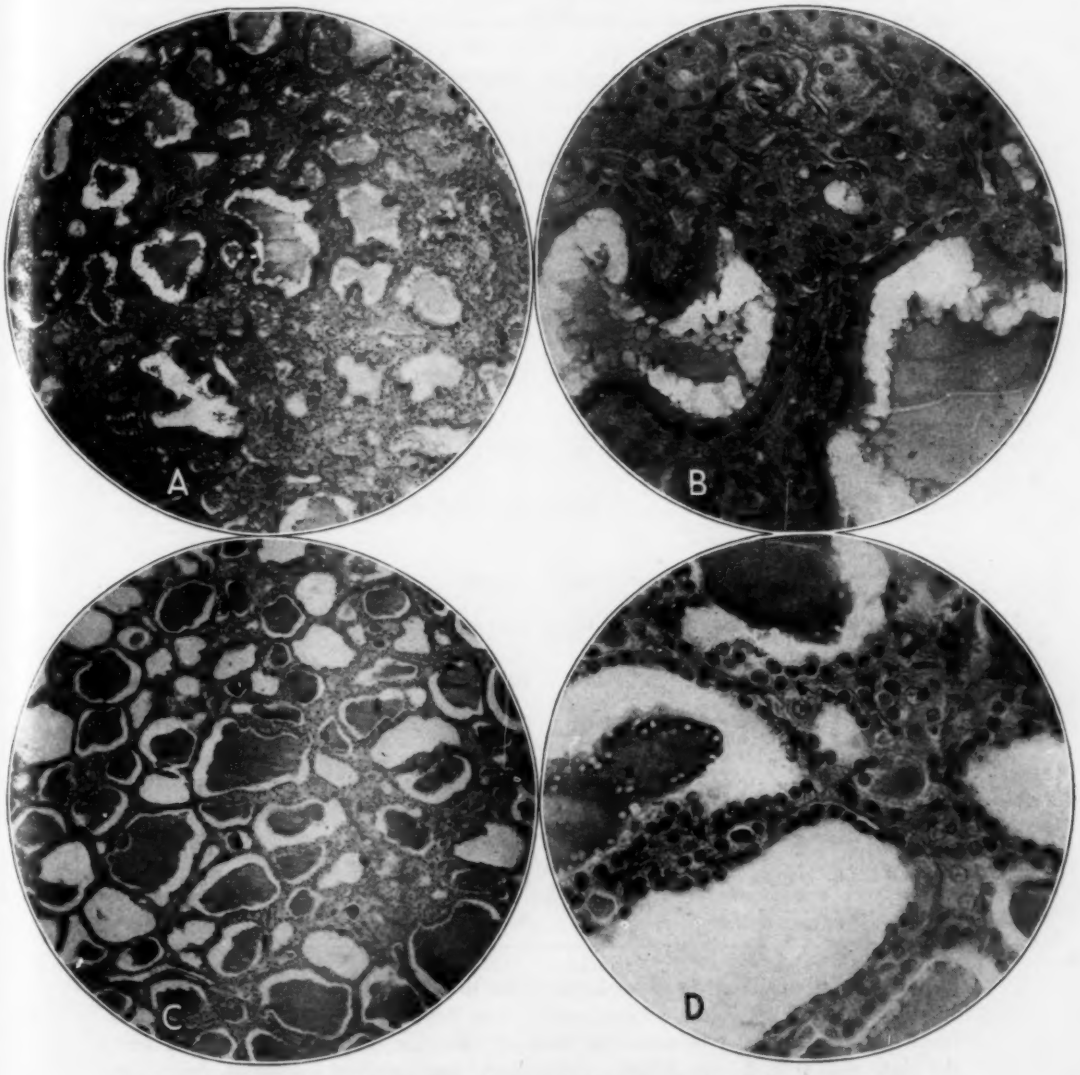

Fig. 2 (dog 61).—*A* and *B* are low and high power photomicrographs of sections of the thyroid gland before implantation of an infected foreign body into the muscles of the neck of a dog, and *C* and *D* are two corresponding magnifications of sections taken fifty days after implantation. Seeing *C* and *D* alone, one might suspect that the thyroid gland in this dog is more active than normal, but with the control there is no doubt that no histologic change has occurred. Note the tiny vesicles (supposed to be absorption vesicles) in the colloid in *C* and *D*.

the operation and are not considered in the report. Three died in from nine to eleven days. There was no suggestion of nervousness or excitability in the dogs. They looked apathetic and sluggish. Those that lived were killed individually in from five to one hundred and twenty-seven days by electrocution. A complete autopsy was done, and the thyroid and adrenal glands were measured and sectioned for microscopic examination. The adrenal glands of animals killed within two weeks showed the result of contusion; those of the animals killed later in some

TABLE 2.—*Results of Crushing the Adrenal Glands*

Dog No.	Initial Weight, Kg.	Method	Interval After Injury to Adrenal Gland, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
24	13.7	Entire left and ⅔ of right adrenal gland crushed	5	Looked sick; moved slowly; moribund; killed	No change in thyroid
14	7.1	Entire left adrenal gland crushed	6	Thin; emaciated; looked sick; killed	No change in thyroid; left adrenal ⅔ macerated
25	13.8	Entire left and ⅔ of right adrenal gland crushed	9	Looked normal; killed	No change in thyroid; both adrenals partially destroyed
26	6.6	Entire left and ⅔ of right adrenal gland crushed	10	Sick; died	No change in thyroid; ½ right adrenal remained; no left adrenal
33	...	½ of right and entire left adrenal gland crushed	10	Sick; died	No change in thyroid
29	7.5	Entire right and ⅔ of left adrenal gland crushed	11	Emaciated; died	No change in thyroid; left adrenal ½ normal; right, ⅓ normal size
13	3.9	Entire right adrenal gland crushed	11	Healthy	No change in thyroid; right adrenal missing
8	8.2	Entire left and ⅓ of right adrenal gland crushed	14	Sick; moves slowly	No change in thyroid
8	8.2	.....	103	Healthy	No change in thyroid; adrenals normal size
7	7.5	Entire right and ⅓ of left adrenal gland crushed	14	Sick; moves slowly	No change in thyroid
7	7.5	.....	117	Healthy	No change in thyroid
5	7.1	Entire left and ¼ of right adrenal gland crushed	24	Weak; moves slowly	No change in thyroid; died; no cause found; regeneration of adrenals
6	6.4	Entire left adrenal gland crushed	24	Weak	No change in thyroid
6	6.4	.....	127	Normal	No change in thyroid

instances were smaller than normal, but in all the animals the wounds had healed. In three animals (6, 7 and 8) exploration was done to obtain a biopsy specimen from the thyroid gland between the time of operation on the adrenal gland and the date the animal was killed. Subsequent sections were obtained from the thyroid glands of twelve animals in the following periods after the operation on the adrenal glands: five, six, nine, ten, ten, eleven, eleven, fourteen, fourteen, twenty-four, twenty-four, one hundred and three, one hundred and seventeen and one hundred and twenty-seven days, respectively.

Comparison of the gross measurements and histologic appearance of sections of thyroid gland obtained at the preliminary operation with subsequent sections from the same gland showed no evidence of hyperplasia or retrogression.

FREEZING THE ADRENAL GLANDS AS A STIMULUS TO THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Seven dogs were used in an attempt to show whether freezing the adrenal glands would produce hyperplasia of the thyroid gland (table 3). At a preliminary operation the thyroid gland of each dog was measured, and a small piece of tissue, 2 by 2 mm., was removed from the right lobe. This was stained as a normal section with which to compare later sections. After the preliminary wound had healed, each adrenal gland was exposed by a lumbar incision and frozen solidly with a spray of ethyl chloride for several minutes. The wound was then closed. One animal died in four days as a result of this procedure. They were all sick, sluggish and apathetic and lost weight. The remaining animals were killed after thirteen, fourteen, nineteen, twenty-five, seventy-one and eighty-five days, respectively. The measurements and microscopic appearance of the thyroid glands were compared with those obtained at the preliminary operation. At necropsy the adrenal glands showed hemorrhage grossly and microscopically. Petechiae were still present in the adrenal glands of the animal killed twenty-five days after freezing. Moreover, in some instances the glands seemed to remain smaller than normal.

TABLE 3.—*Results of Freezing Adrenal Glands*

Dog No.	Initial Weight, Kg.	Method	Interval After Freezing Adrenal, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
47	4.9	Both adrenal glands frozen	4	Sick; died	No change in thyroid; adrenals hemorrhagic
32	9.4	Both adrenal glands frozen	13	Sick, sluggish and emaciated; killed	No change in thyroid; left adrenal infected
45	7.4	Both adrenal glands frozen	14	Normal	No change in thyroid; adrenals ⅓ normal size
31	7.0	Both adrenal glands frozen	19	Normal	No change in thyroid; petechiae in right adrenal; hyaline degeneration in left
46	6.8	Both adrenal glands frozen	25	Emaciated; sluggish	No change in thyroid; left adrenal showed petechiae
44	5.5	Both adrenal glands frozen	71	Thin; apathetic	No change in thyroid; left adrenal normal; right adrenal ⅓ normal size
43	5.6	Both adrenal glands frozen	85	Normal	No change in thyroid; adrenals slightly smaller than normal

In no instance was there gross or microscopic evidence of hyperplasia or retrogression of the thyroid gland.

HIGH CALCIUM CHLORIDE INTAKE AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Six dogs were used in experiments on the effect of a high calcium chloride intake on the thyroid gland (table 4). At a preliminary operation the thyroid gland of each dog was measured, and a small piece of the right lobe, 2 by 2 mm., was removed for microscopic study. Four animals were given 2 per cent calcium chloride in distilled water. They refused to drink this concentrated solution, and

after five days they were given 500 cc. of the solution twice daily, by stomach tube. Because all of the dogs suffered from continued vomiting after four days of this regimen and after one of the dogs (65) died, 0.05 per cent calcium chloride in distilled water was used as drinking water for the remainder of the experiment. Two other dogs (68 and 69) were started on this solution as their only drinking water immediately after the preliminary operation. Four of the six dogs died after six, seven, twelve and ninety-six days, respectively. The remaining two were killed

TABLE 4.—*Results with a High Calcium Intake*

Dog No.	Initial Weight, Gm.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
68	3.8	Calcium chloride 0.05%	6	Died	Hyperplasia (?)
65	7.8	Calcium chloride 2%, 500 cc. daily	7	Sick: died	Smaller acini; less colloid
66	10.2	Calcium chloride 2%, 500 cc. daily	12	Sick; died	No change
69	6.6	Calcium chloride 0.05%	80	Healthy	Definite hyperplasia
64	10.3	Calcium chloride 2%, 500 cc. daily for 8 days and 0.05% for 88 days	96	Sick; died	Hyperplasia (?); postmortem degeneration
67	10.1	Calcium chloride 2% for 8 days and 0.05% for 105 days	113	Healthy	Definite hyperplasia

TABLE 5.—*Blood Calcium Determinations on Dogs Drinking Calcium Water*

Dog No.	Preliminary Estimation of Blood Calcium, Mg.		Date of Starting Experiment	Subsequent Calcium Determinations, Mg.
	High	Low		
68	10.12	10.06	July 17	July 23, death
65	10.78	10.62	June 14	June 15, 10.52; June 20, 11.01; June 22, death
66	11.19	10.92	June 14	June 15, 11.48; June 20, 11.21; June 26, death
69	11.42	11.42	July 17	July 27, 10.98; August 2, 11.14; August 9, 12.78; August 16, 11.48; August 23, 12.49; August 30, 14.20; September 6, 11.32; September 13, 12.03; September 20, 10.92; September 27, 11.46; October 4, 12.33; October 5, killed
64	10.90	10.51	June 14	June 15, 11.58; June 21, 11.96; June 27, 11.14; July 3, 11.14; July 10, 11.14; July 27, 10.51; August 2, 11.14; August 9, 12.78; August 16, 9.64; August 23, 9.49; August 30, 10.12; September 6, 8.82; September 13, 8.69; September 17, necropsy
67	11.33	10.90	June 14	June 15, 11.2; June 20, 14.61; June 27, 11.28; July 3, 11.28; July 10, 11.14; July 27, 10.51; August 2, 11.14; August 9, 12.78; August 16, 11.64; August 23, 12.25; August 30, 11.70; September 6, 10.17; September 13, 11.23; September 20, 10.92; September 27, 10.26; October 4, 10.64; October 5, killed

after drinking the calcium water for eight and one hundred and thirteen days, respectively. At necropsy the thyroid gland of each animal was measured. Sections stained with hematoxylin and eosin were compared with the original sections removed at the preliminary operation.

Prior to initiating the experiment, determinations were made on the blood calcium in each dog on at least two different days. During the course of the experiment, while the dogs were taking the calcium solution, determinations were made on the blood calcium once a week. The calcium content of the blood was

elevated from 0.5 to 2 mg. by the inhibition of calcium chloride drinking water, but as may be seen from table 5 the elevation was not constant. Determinations were made after the food was removed from the cages over night and the dogs were permitted to drink calcium chloride water.

Gross measurements of each gland showed no appreciable difference between the measurements made at necropsy and those made at the preliminary operation, but microscopically the changes were striking (fig. 3), not only in isolated or selected areas but throughout the gland. There was evidence of hyperactivity as indicated by less colloid in the vesicles, even to complete disappearance; large columnar epithelium, and marked vesicular changes in the colloid, not only at the periphery but throughout the entire acini, so that the colloid looked as if it had degenerated into bubbles. No changes were found in the thyroid glands of dogs dying after seven and twelve days, respectively. There were questionable changes in the thyroid gland in the dog that died after six days, and definite changes in the glands of dogs that died after eighty, ninety-six and one hundred and thirteen days.

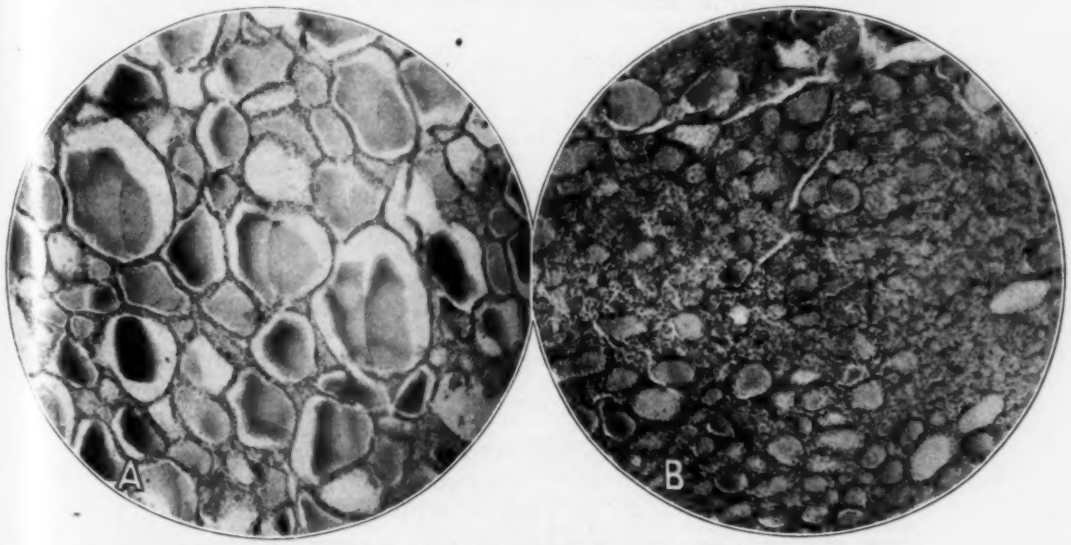

Fig. 3 (dog 67).—*A* is a preliminary section from the thyroid gland of a dog. *B* is a section from the thyroid of the same dog taken one hundred and thirteen days later, after drinking 0.05 per cent calcium chloride water during that interval. The magnification is the same as that of *A*. The entire microscopic appearance has changed. From flat epithelium lining the acini in *A*, the epithelium has changed to a more cuboidal form in *B* but seems in some instances to be several layers thick. The acini are smaller in *B*, and numerous tiny vesicles are found throughout the colloid. These are representative of the entire section and are not selective areas.

These experiments indicate that calcium eliminates the colloid from the thyroid gland and increases the size of the epithelium. Thus, from these experimental results, at least, it does not seem that calcium chloride is the cause of colloid goiter but that it does change the histologic appearance of the thyroid gland.

GONADOTROPIC PRINCIPLE FROM THE URINE OF PREGNANT WOMEN AS A STIMULUS TO PRODUCTION OF HYPERPLASIA OF THE THYROID GLAND

Five dogs were used to determine the effect of the gonadotropic principle from the urine of pregnant women on the thyroid gland. At a preliminary operation the thyroid gland of each dog was exposed and measured, and a piece of tissue, 2 by 2 mm., was removed from the right lobe and sectioned to serve as a normal section for comparison. Thereafter, 1 cc. of the gonadotropic principle [37] was injected intraperitoneally daily for the remainder of the experiment. The remaining dogs were killed in six, eleven, twelve, twenty-five and fifty-one days, respectively. At necropsy the thyroid gland of each animal was removed, measured and sectioned. The material was stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog.

In none of the dogs was there any gross or microscopic evidence of hyperplasia or changes in the thyroid gland (table 6). These experiments indicate that the gonadotropic principle has no thyrotropic properties.

TABLE 6.—*Results with Gonadotropic Principle from Urine of Pregnant Women*

Dog No.	Initial Weight, Kg.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
70	6.2	1 cc. of gonadotropic principle daily	6	Healthy	No change
72	5.3	1 cc. of gonadotropic principle daily	11	Sick; distemper	No change
73	4.2	1 cc. of gonadotropic principle daily	12	Healthy	No change
74	3.4	1 cc. of gonadotropic principle daily	25	Healthy	No change
71	6.6	1 cc. of gonadotropic principle daily	51	Healthy	No change

EXPERIMENTS ON GUINEA-PIGS TO TEST THE EFFICIENCY OF ANTERIOR PITUITARY EXTRACT AS A STIMULUS FOR THE PRODUCTION OF CHANGES IN THE THYROID GLAND

Eleven guinea-pigs were used to test the efficiency of anterior pituitary extract in the production of changes in the thyroid gland. The disadvantage in using guinea-pigs is that they are too small for preliminary operation and section of the thyroid gland for comparison with later sections. Therefore, the experiments on these animals are not controlled for individual animals. Guinea-pigs are, however, less expensive. Young guinea-pigs about 3 months of age, weighing between 250 and 400 Gm., were chosen. In each instance at the end of the experiment the guinea-pig was killed by injecting 2 cc. of ether into the heart. The thyroid gland was then exposed and measured. In some instances there was a definite isthmus between the two small thin lobes lying close to the trachea. In other instances the isthmus was rudimentary or absent. The parathyroid glands were embedded in the thyroid gland. The thyroid glands were removed and carefully measured, and each gland was sectioned and stained with hematoxylin and eosin.

37. The gonadotropic principle used was antuitrin-S. It was supplied by Parke, Davis and Company.

In each instance the pituitary gland, the pars anterior and posterior, was removed and sectioned for microscopic study in order to determine whether a pituitary extract affecting the histologic structure of the thyroid gland might also affect the pituitary gland.

Of the eleven guinea-pigs, three were used as controls. They had been kept in the cages for ten, fourteen and sixty-two days, respectively, while their companions were receiving injections of anterior pituitary extract daily. At the time they were killed they weighed 310, 400 and 650 Gm., respectively. These weights gave some basis for comparison of the size of the thyroid glands of those animals which weighed approximately the same but which had been subjected to intraperitoneal injections of anterior pituitary extract.

Eight of the guinea-pigs were given daily intraperitoneal injections of anterior pituitary extract (1 cc.), an extract of the pars anterior of the pituitary gland. No iodine was used in the experiment, and the guinea-pigs were killed after two, four, six, eight, ten, nineteen, thirty-two and sixty-four days, respectively, by injecting 2 cc. of ether directly into the heart. The thyroid and pituitary glands were recovered and compared microscopically with themselves and with the controls. The extract apparently did not produce any abnormal increase in weight. The sixty-six day control, weighing 650 Gm. (initially 400 Gm.), was compared with guinea-pig 6, weighing 600 Gm. (initially 400 Gm.), after sixty-four daily injections of anterior pituitary extract. Similar comparisons to show this point may be seen in the protocol.

Results of the experiment show that the extract apparently produces some gross change in the thyroid gland. Although the method of measurement was crude, the thyroid gland of the guinea-pig (weight, 600 Gm.) that had received the extract for sixty-four days was slightly greater than that of the control guinea-pig (weight, 650 Gm.) which had been observed for sixty-six days. Similar comparison may be made with other animals in the series with a control of analogous weight. There was no apparent change in the conformity of the gland, and the difference in size detectable by this method is not accepted as unequivocal proof that there is a gross change under these circumstances.

In every instance the pituitary gland showed no recognizable changes microscopically. However, in the thyroid glands from the animals which had received a large number of injections there was unquestionable evidence of hyperplasia (fig. 4). This evidence was seen not only in selected areas but throughout the sections. The microscopic changes indicative of hyperplasia were:

1. The vesicles were smaller and contained less colloid. This reduction in colloid was approximately one third of that in the acini of the controls.

2. In the colloid of the normal guinea-pig, after the thyroid gland was sectioned and stained with hematoxylin and eosin, minute, apparently clear, rounded vesicles were found. These were near the periphery of the colloid. They may be interpreted as evidence of colloid absorption, but this has not been established unequivocally as an accurate interpretation. However, in the guinea-pigs which had received daily doses of anterior pituitary extract over a prolonged period and in which the colloid in the vesicles was diminished, these vesicles were much more numerous and larger and in some instances (guinea-pig 16) were so plentiful that practically all the remaining colloid seemed to be nothing but bubbles.

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38. The anterior pituitary extract used was antuitrin. It was supplied by Parke, Davis and Company.

3. I do not believe that the sign of basophilic staining of the colloid is reliable as a guide to absorption of colloid or hyperactivity of the thyroid gland. It is true that a bluish tinge to the colloid does occur. It was found in the animals that had received anterior pituitary extract over a long period of time, but I also

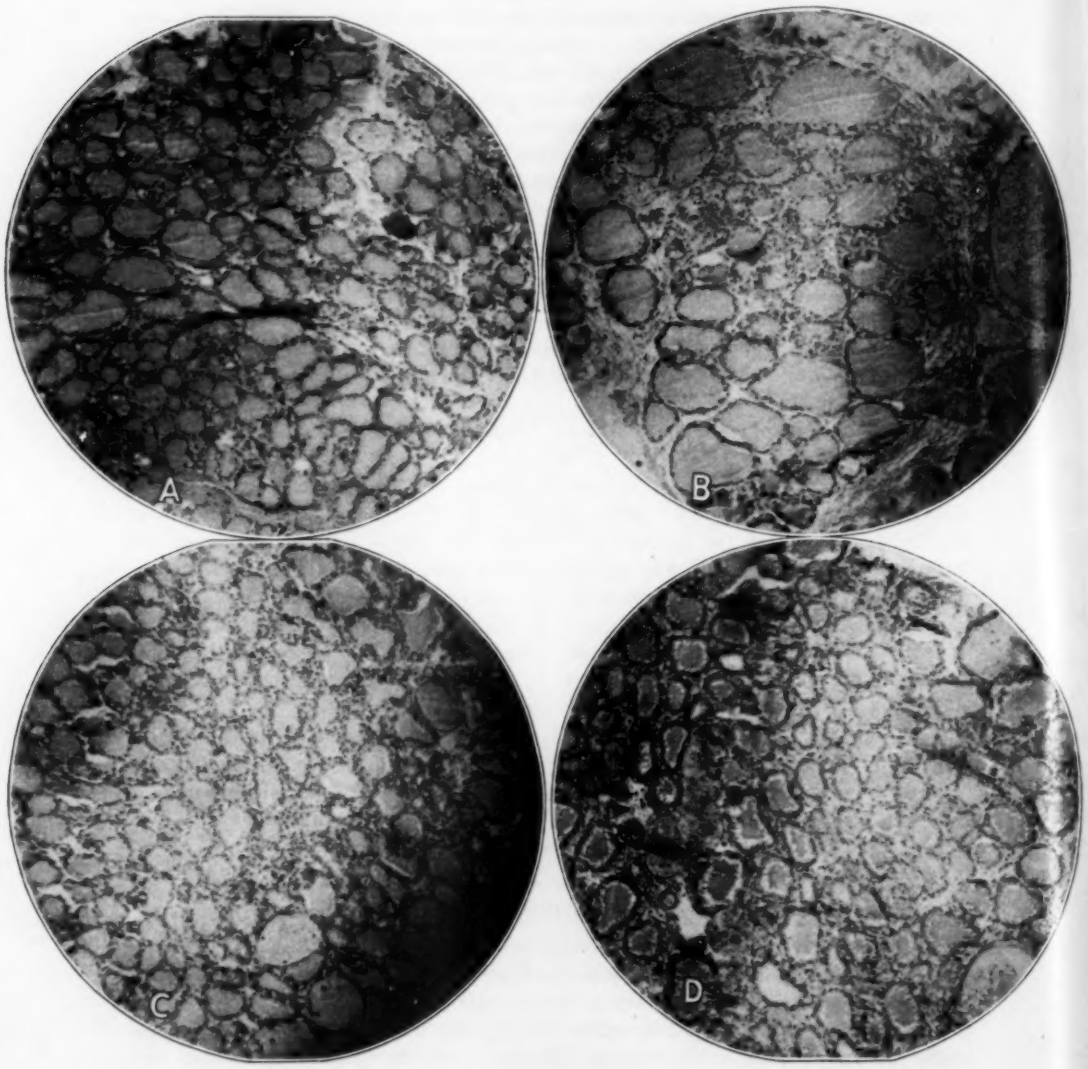

Fig. 4.—Photomicrographs (all identical magnification) of sections of the thyroid gland of four different guinea-pigs. *A* and *B* are sections from normal controls. *C* is a section from the thyroid gland of a guinea-pig which had received daily intraperitoneal injections of anterior pituitary extract for nineteen days. *D* is a section from a guinea-pig which had received injections of anterior pituitary extract daily for ten days. *C* and *D* show smaller acini, more cuboidal cells, less colloid and more vesicles in the colloid than the sections from the controls. The changes in the ten day section are more marked than those in the nineteen day section, but the length of administration does not parallel the degree of change.

found it in some areas in the normal controls. Some normal glands exhibited basophilic colloid more than others, and whereas it seemed to be more constant in animals which had received the extract, its presence is so unreliable in its associations that using it as a sign of activity carries only the weight of presumption.

4. The cells lining the acini of the thyroid gland were definitely more columnar in the animals which had received the extract. The flattest cell in the animals receiving the extract was more columnar than the tallest cells in the acini of the controls. In some acini of the thyroid glands which had been stimulated by

TABLE 7.—*Results with Anterior Pituitary Extract*

Guinea-Pig No.	Stimulus	Duration of Experiment, Days	Weights, Gm.		Clinical Appearance of Dog	Thyroid Gland		Microscopic Appearance of Pituitary Body
			Initial	Final		Measurements	Microscopic Appearance	
10	Control	10	300	310	Healthy	R.: 1.0x0.4 cm. L.: 0.9x0.3 cm.	Normal	Normal
1	Control	14	400	400	Healthy	R.: 0.8x0.5 cm. L.: 1.0x0.5 cm.	Normal	Normal
2	Control	66	400	650	Healthy	R.: 1.3x0.6 cm. L.: 1.5x0.5 cm.	Normal	Normal
12	Anterior pituitary extract, 1 cc. daily intraperitoneally	2	220	300	Healthy	R.: 0.7x0.3 cm. L.: 0.6x0.3 cm.	Slight (?) hyperplasia	Normal
13	Anterior pituitary extract, 1 cc. daily intraperitoneally	4	340	380	Healthy	R.: 1.0x0.5 cm. L.: 1.0x0.3 cm.	Questionable hyperplasia	Normal
14	Anterior pituitary extract, 1 cc. daily intraperitoneally	6	260	300	Healthy	R.: 1.0x0.3 cm. L.: 1.0x0.4 cm.	Questionable hyperplasia	Normal
15	Anterior pituitary extract, 1 cc. daily intraperitoneally	8	260	320	Healthy	R.: 1.0x0.3 cm. L.: 1.0x0.4 cm.	Slight hyperactivity	Normal
16	Anterior pituitary extract, 1 cc. daily intraperitoneally	10	260	320	Healthy	R.: 1.2x0.4 cm. L.: 1.5x0.5 cm.	Definite hyperactivity	Normal
4	Anterior pituitary extract, 1 cc. daily intraperitoneally	19	420	335	Healthy	R.: 0.9x0.3 cm. L.: 1.0x0.5 cm.	Hyperactivity	Normal
5	Anterior pituitary extract, 1 cc. daily intraperitoneally	32	330	300	Healthy	R.: 1.0x0.5 cm. L.: 0.9x0.5 cm.	Hyperactivity	Normal
6	Anterior pituitary extract, 1 cc. daily intraperitoneally	64	400	600	Healthy	R.: 1.5x0.5 cm. L.: 1.6x0.5 cm.	Normal	Normal

the anterior pituitary extract there were high columnar epithelial cells similar to the epithelial cells lining the follicles in the thyroid of a patient with exophthalmic goiter. In no instance were there any infoldings or papillary projections.

The most marked evidences of hyperactivity in these sections occurred in the animals receiving the injection for from ten to thirty-two days. It had disappeared in the sixty-four day specimen. Several authors [39] have reported evidence indicating that continued injection of extract of the anterior lobe of the pituitary gland produces changes in the thyroid gland which retrogress toward the normal after different periods of time.

39. Loeb and Friedman.[25] Siebert and Thurston.[29] Collip and Anderson.[35]

COMMENT

The conclusions to be drawn from these experiments are merely supportive or nonsupportive of certain still controvertible ideas that extraneous substances stimulate or inactivate the thyroid gland in such a manner as to produce goiter. The experiments support strongly the view that the excess administration of calcium chloride results in changes in the histologic appearance of the thyroid gland. These changes indicate hyperactivity. These experiments do not corroborate the findings of other investigators that infection in the organism and injury to the adrenal gland affects the histologic picture of the thyroid gland.

At the present time these are all merely accumulations of facts which may encourage one to believe that an explanation of the etiology of goiter is nearer. It is still debatable whether the true cause is positive and extraneous, such as calcium or an unknown goitrogenic substance, or positive and autogenous, such as a hormone of the pituitary gland, or negative and autogenous, such as the absence of a hormone, or negative and exogenous, such as a deficiency of some necessary exogenous regulator, for example, iodine. Many conflicting data exist in the literature on the etiology of goiter, but in the main the accumulating weight of evidence is that a hormone of the anterior lobe of the pituitary gland can stimulate the thyroid gland to hyperactivity. It is a much further step to prove that this hormone is the factor outside the thyroid gland which whips it up to hyperactivity in acute hyperthyroidism. It is my experience, as well as that of others, that the thyroid gland removed at operation for hyperthyroidism in patients with acromegaly is a meaty type of thyroid, very parenchymatous and with relatively little colloid in the follicles. In comparing the clinical with the experimental evidence, the interesting question arises whether hyperthyroidism in cases of acromegaly, which is akin to, but clinically not exactly the same as, exophthalmic goiter, results from long-continued excess of this particular thyrotropic hormone of the anterior lobe of the pituitary gland, or whether exophthalmic goiter actually is acute acromegaly or at least a fraction of it. Experimental evidence has far from answered this question.

At the present time there are other possible factors with as much accumulated experimental support, if not in quantity at least in quality. Calcium, an entirely extraneous factor, undoubtedly produces changes in the thyroid gland. Will excess calcium be responsible for one type of goiter and the anterior pituitary extract for another?

Iodine undoubtedly is a factor, but it appears to be an objective and not a subjective one. It is lessened in the goitrous gland, but it seems that something else either fixes it in the blood stream to prevent it from being utilized by the gland or drives it out of the gland by the

hyperactivity of the parenchyma. It is true that even when the intake of iodine is undoubtedly adequate under ordinary conditions, the thyroid gland may undergo changes histologically and functionally. Iodine in excess of the normal intake may mitigate the action of the additional factor, but the additional factor is the important one, and that factor as yet has not been found with certainty.

SUMMARY

Experiments on dogs and guinea-pigs gave results which might be safely interpreted to support the following conclusions: Infection in the organism has no specific effect on the histologic picture of the stage of activity of the thyroid gland or on the size of the gland. Injury to or freezing of the adrenal gland in a series of animals resulted in no gross or microscopic changes in the thyroid gland, thus intercepting the inference that elevated basal metabolic rates after similar procedures in the lower animals are the result of hyperthyroidism.

Anterior pituitary-like gonadotropic substances obtained from the urine of pregnant women had no effect on the histologic structure of the thyroid gland when injected daily over varying periods of time. But an extract of the anterior lobe of the pituitary gland produced a histologic picture in the thyroid gland which might be interpreted as increased activity of the gland, viz., disappearance of colloid or diminution of the amount of colloid in the acini; an increase in the size of the epithelial cells, changing their form from low cuboidal to high columnar epithelium, and an increase in the number of vacuoles in the colloid, possibly an indication of its absorbability.

Calcium chloride when added to the drinking water produced definite histologic changes in the thyroid gland of animals which had been on the regimen eighty days or longer. The histologic changes were similar to those described as the result of the administration of anterior pituitary extract; viz., less colloid, larger epithelial cells and more vacuoles in the remaining colloid.

CONGENITAL DISLOCATION OF THE SHOULDER AND OTHER ANOMALIES

REPORT OF A CASE AND REVIEW OF THE LITERATURE

LEWIS COZEN, M.D.
SAN FRANCISCO

A case is presented of dislocation of both shoulders since birth. Whether the deformity was truly congenital in the sense of an intra-uterine maldevelopment or whether it was incidental to trauma at birth cannot be stated with certainty. Many dislocations reported as congenital, that is, as intra-uterine, are of paralytic origin or are possibly caused by trauma at birth. The case presented here illustrates the difficulty that arises in determining the etiologic factor of "congenital dislocations of the shoulder." Because of several other rare deformities, namely, amyoplasia congenita, congenital radio-ulnar synostoses, ectrodactylia and cervical ribs, this case assumes added interest.

Some authors (Kirmisson and Broca) have been unable to produce dislocation of the shoulder joint experimentally in a new-born child and hence have concluded that a dislocation cannot result from the trauma of birth. There is no doubt, however, that paralysis caused by injury to the brachial plexus will cause or accompany dislocation of the shoulder. Dislocations due to paralysis or to trauma at birth may be differentiated from truly congenital dislocations (1) by the history of an abnormal, a difficult or an unusual instrumental delivery; (2) by the presence of paralyzed or paretic muscle groups in the involved extremity or (3) by the absence of other definitely congenital anomalies which favor the congenital nature of the deformity. Because the differentiation of the two types of dislocations is by exclusion, it is frequently difficult and at times impossible to classify a given case properly.

Greig [1] in 1923 thoroughly reviewed the literature on congenital dislocations of the shoulder, judging the truly congenital nature of the dislocations by the birth history, the presence or absence of paretic musculature and the condition of the child immediately after birth. He found twelve reported cases in which there was no doubt in his mind that the deformity was a primary intra-uterine developmental defect. Many dislocations of secondary types, comprising the disloca-

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From the State University of Iowa, College of Medicine, Department of Orthopedic Surgery, service of Dr. Arthur Steindler.

1. Greig, D. M.: True Congenital Dislocation of Shoulder, Edinburgh M. J. **30**:157-175 (April) 1923.

tions associated with the trauma of birth, are seen in orthopedic clinics and practices.

A critical survey of the cases reviewed by Greig leads me to include only ten instead of twelve cases as instances of truly congenital dislocation. In the cases recorded by Abadie and Pelissier,[1a] Cumston,[2] Hebert,[3] Hitzrot,[4] Kelley,[5] Léniez,[6] Openshaw,[7] Peckham [8] and Scudder [9] (two cases) the condition can be neither of traumatic nor of paralytic origin. Küster's [10] patient had a spastic upper extremity. The history of the birth is not mentioned in his report, and the condition seems to be spastic paralysis with associated dislocation of the humerus. Hartwell's [11] description discloses paralysis of the deltoid muscle, so that his case cannot be placed in the group of instances of primary dislocation.

Since the publication of Greig's series in 1923, eight additional cases of this deformity have been reported; seven are instances of the truly congenital type, and the origin of the dislocation in the other is doubtful.

Frosch [12] in 1925 presented three cases, in each of which the dislocation was bilateral. He expressed the belief that the abscence of trauma at birth and of muscular paralysis eliminated the possibility that the dislocation was anything but a developmental anomaly. Roentgenograms of the three patients showed an abnormally flattened glenoid fossa. This anomaly was also bilateral in all three patients.

1a. Abadie, J., and Pelissier, G.: Luxation congénitale de l'épaule, Rev. d'orthop. **1**:245-260 (March) 1910.

2. Cumston, C. G.: Congenital Dislocation of the Shoulder, Am. J. M. Sc. **125**:967-984 (June) 1903.

3. Hebert, P.: Absence congénitale des voies biliaires extra-hépatiques chez un enfant d'un mois présentant en outre un persistance du trou de Botal, et une malformation congénitale du membre supérieur gauche, avec luxation de l'épaule, absence du radius et main bote cubitale, Rev. d'orthop. **5**:57-66 (Jan.) 1904.

4. Hitzrot, J. M.: Posterior Congenital Dislocation of the Left Shoulder, Ann. Surg. **55**:622-623 (April) 1912.

5. Kelley, S. W.: Surgical Diseases of Children, ed. 3, St. Louis, C. V. Mosby Company, 1929.

6. Léniez: Un cas de luxation congénitale de l'épaule, Rev. d'orthop. **10**:159-164 (March) 1909.

7. Openshaw, T. H.: Case of Multiple Dislocation, Including Congenital Dislocation of Both Hips, in a Child Aged Two Weeks, Incontestably the Result of Malposition in Utero, Proc. Roy. Soc. Med. (Clin. Sect.) **1**:106, 1907-1908.

8. Peckham, F. E.: Two Cases of Congenital Dislocation of the Shoulder Joint, Arch. Pediat. **21**:509-511 (July) 1904.

9. Scudder, C. L.: Congenital Dislocation of the Shoulder-Joint: Report of Two Cases, Arch. Pediat. **7**:260-269 (April) 1890.

10. Küster, E.: Ein 1 jähriges Kind mit angeborenen doppelseitiger Luxation des Oberarmkopfes nach hinten, Berl. klin. Wchnschr. **16**:9 (Jan. 6) 1879.

11. Hartwell: Deformity of the Shoulder. Joint, Ann. Surg. **45**:454 (March) 1907.

12. Frosch, L.: Congenital Subluxation of Shoulders, Klin. Wchnschr. **4**:701-702 (April 9) 1925.

A case of bilateral dislocation of the humerus was reported in 1928 by Edwards.[13] Autopsy on this man, who was 46 years of age, revealed the glenoid fossa to be absent, its place being taken by the neck of the scapula. The biceps tendon (long head) arose from a point corresponding to the supraglenoid tubercle. Although his delivery was said to have been difficult, there was no accompanying paralysis. Here is another case similar to the one I am reporting, in which the dislocation cannot be classified with surety as a congenital anomaly. The difficult birth casts a shadow of doubt on its intra-uterine causation despite the developmentally retarded shoulder joint disclosed at autopsy.

The next case to be found in the literature is that of Wolff,[14] who in 1929 described a patient in whose family a similar deformity had been known for the previous three generations. Other anomalies, such as absence of a thumb and amniotic bands, were present. There was, in addition, rigidity of the elbows and interphalangeal joints, apparently congenital, with absence of motion in the radio-ulnar articulations. This description practically duplicates that of my patient. The author does not comment on the presence of the congenital articular rigidity, although his case is apparently the first ever reported in which both anomalies were present—congenital dislocation of the shoulder and congenital articular rigidity (arthrogryposis, multiple congenital contractures and amyoplasia congenita). If the dislocation in the case presented here is truly congenital, then the case will be the second in the literature in which both deformities are reported.

To Valentin[15] is credited the report of three cases in one family, which he described in 1931. The two brothers and one sister had varying degrees of functional inpairment of their arms, but in none was the malfunction severe. In all three roentgenograms revealed posterior dislocation of the head of the humerus and flattening of the glenoid fossa. Birth was normal in each of the siblings.

Can the following case be added to this small group of true congenital dislocations?

REPORT OF CASE

L. C., a boy, was brought to the orthopedic clinic at the State University of Iowa at the age of 4 years because of the abnormal appearance and weakness of both his upper extremities. He has three brothers, all older than he and none with any known abnormalities. An infant who would have been his uncle was stillborn, with "deformed feet and ankles." No other deformity was revealed in the familial history.

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13. Edwards, H.: Congenital Displacement of Shoulder Joint, J. Anat. **62**: 177-182 (Jan.) 1928.

14. Wolff, G.: Ueber einen Fall von kongenitaler Schulterluxation, Ztschr. f. orthop. Chir. **51**:199-209 (Jan. 11) 1929.

15. Valentin, B.: Die kongenitale Schulterluxation, Bericht über drei Fälle in einer Familie, Ztschr. f. orthop. Chir. **55**:229-240, 1931.

The patient's mother stated that his delivery was "long and hard" and that he weighed 13½ pounds (6,123 Gm.). A forceps was not used. His neck was encircled twice by the umbilical cord; he did not cry for twenty minutes after birth. His arms and hands "did not look right" immediately after birth, his mother affirmed. When he was 2 months of age a rudimentary right thumb was removed by the family physician.

When the patient first entered the clinic, eight years before the present examination, several abnormalities were noted. The clavicles were extremely prominent, and their normal curvature was increased. Both shoulders had a squared instead of the usual rounded appearance. This squaring of the shoulders was caused by the accentuated acromion processes with the displacement of the heads of the humeri inferiorly, out of the glenoid cavities. On the left shoulder there was a gap of about 2 inches (5 cm.) between the head of the humerus and the acromion process.

Fig. 1.—*A*, the boy as he appeared on his first visit to the clinic. The humeri were not abducted to their maximum, but merely enough to depict the hands clearly. *B*, photograph taken on March 1, 1933, after capsulotomy on both shoulder joints, augmented by a Nicola suspension operation on the head of the right humerus.

Motion in the shoulder joints in degrees was as follows:

	Right	Left
Flexion	0- 95	0- 90
Extension	0- 15	0- 10
Abduction	0-120	0-100
Adduction	0- 25	0- 25
External rotation	0- 30	0- 20
Internal rotation	0- 10	0- 20

There were slight atrophy and weakness of the shoulder muscles on both sides, that is, the deltoid, pectoralis major, latissimus dorsi, supraspinatus, infraspinatus, biceps and triceps muscles.

A flexion contracture of 30 degrees was found in the left elbow, and of 10 degrees in the right, so that the angle of maximum extension on the right elbow was 170 degrees, and of maximum flexion, 30 degrees. On the left side the values were, respectively, 150 and 40 degrees. Pronation and supination movements in the forearms were absent; the left forearm was fixed in a position of 50 degrees of pronation, and the right was held in a neutral or pistol grip position.

There was no limitation of motion in the wrist joints proper. There was dorsiflexion of from 180 to 135 degrees and palmar flexion of from 180 to 110 degrees. The range of motion in the two wrists was practically identical.

The entire first ray of the right hand was absent; no metacarpal or phalanges of the thumb were present. On the left hand there were a diminutive first metacarpal and two phalanges attached to the index finger at the base of its first phalanx. The boy could not control this digit voluntarily.

Motion in the fingers was limited as follows:

	Right	Left	Normal
Metacarpophalangeal joints	180-140	180-150	180-90
First interphalangeal joint.....	180- 95	180-130	180-80
Second interphalangeal joint.....	180-165	175-180	180-90

There was slightly less motion in the digits on the radial side of the hand than in those on the ulnar side.

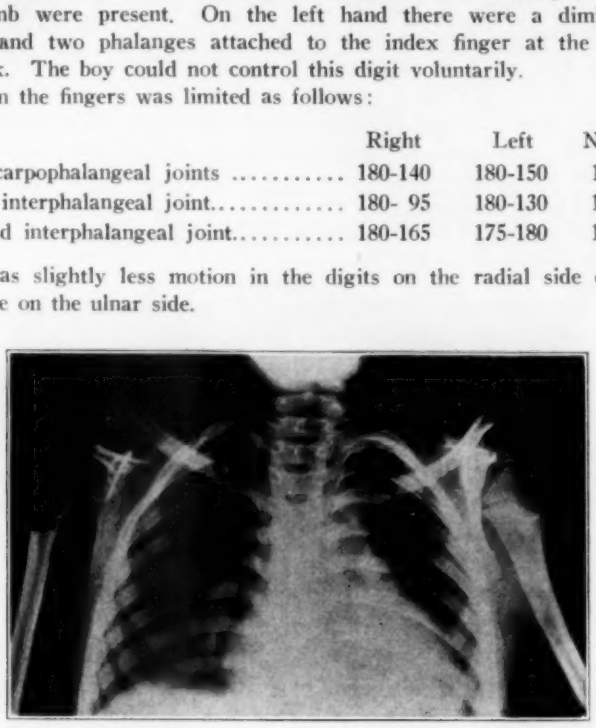

Fig. 2.—Roentgenogram taken on Aug. 8, 1932, four years after capsulotomy on both shoulder joints and one month after the Nicola type of operation of the right shoulder. The pyramidal-shaped heads of the humeri and the shallow glenoid fossae are evident. The rudimentary seventh cervical ribs can be seen.

Both lower extremities were normal; there was no limitation of motion in any of their joints. Only one additional anomaly was found on clinical examination—a patent ductus arteriosus which was causing no symptoms.

Roentgenograms showed maldevelopment of the glenoid fossae with small scapulae, but with large coracoid processes. The heads of the humeri were found to be hypoplastic, especially on the right, where the head was more pyramidal than spherical and was quite a distance below and lateral to the glenoid fossa. Rudimentary seventh cervical ribs were present bilaterally. The upper end of the right ulna appeared deficient anteriorly where the coronoid process formed only a small and flat bony prominence; the semilunar cavity was shallow. The upper radio-ulnar joint appeared to be fused by a bony bridge. Roentgenograms of the left upper extremity were practically identical with those of the right. No other changes were present in the joints of the elbows, wrists and hands.

Operative reefing of the capsules was performed on the right and left shoulder joints. The right shoulder was operated on four weeks after the boy was admitted to the clinic, and the left, eight weeks after his entry. Dislocation recurred spon-

taneously on the right side three years after operation. A typical Nicola suspension operation was performed on the right shoulder in July 1932, four years after the reefing operation. At the time of the second operation it was found that relaxation of the capsule had recurred. The right joint has remained in place since the second operation, but the boy complained of an occasional slipping sensation until one year prior to the present examination (June 2, 1936). Since then he has noted no feeling of instability in the joint and is well pleased with the results of the operations. The left shoulder has remained in the glenoid fossa ever since the capsular reefing was performed in 1929. Despite the mild limitation of motion in the shoulder joints, the boy now has excellent function of both shoulders.

The rudimentary left thumb was removed in 1928, since it was useless and interfered with flexion of the other fingers.

When the patient was examined on June 2, 1936, the only changes that could be noted from his examination eight years previously were the results of the surgical procedures and the increase in size of his entire body. The heads of the humeri were found in close proximity to the glenoid fossae, both on direct and on roentgenographic examination. The relaxation and dislocation had been replaced by stability of the joints in their entire range of motion. Other joints were practically unchanged (they had the same degree of mobility), but there had been

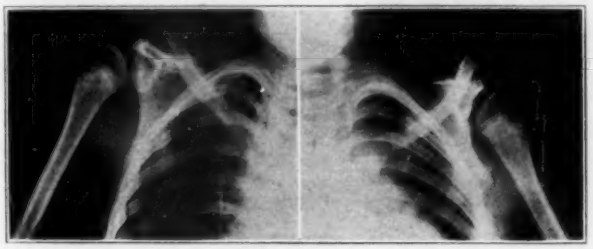

Fig. 3.—Roentgenograms taken on June 2, 1936. The heads of the humeri are rounder, and the humeri and the glenoid fossae are less abnormal than when the first roentgenograms were taken.

an increase in muscular strength of the shoulder girdle, so that now muscle strength was within normal limits. The patient performs many varieties of manual tasks but has slight awkwardness in grasping tools.

The diagnosis, then, is dislocation of the shoulders, with multiple congenital anomalies, namely, contracture of the joints, synostosis of the radius and ulna, ectrodactylism, cervical ribs and a patent ductus arteriosus.

What was the cause of the dislocated shoulders in this patient? He weighed 13½ pounds at birth, and labor was abnormally difficult. Paralysis of the brachial plexus may be discarded as the cause of the dislocation, since no paralyzed muscle could be found. Trauma at birth cannot be so easily disregarded. The prolonged and arduous labor, plus the large weight at birth, point to trauma as the etiologic factor. It has been noted that experimentally it is impossible to produce a traumatic dislocation in a new-born child. The presence of numerous congenital deformities and the deformed glenoid fossae greatly increase the probability of the congenital nature of the deformity. No certain classification of the anomaly as being congenital can be made.

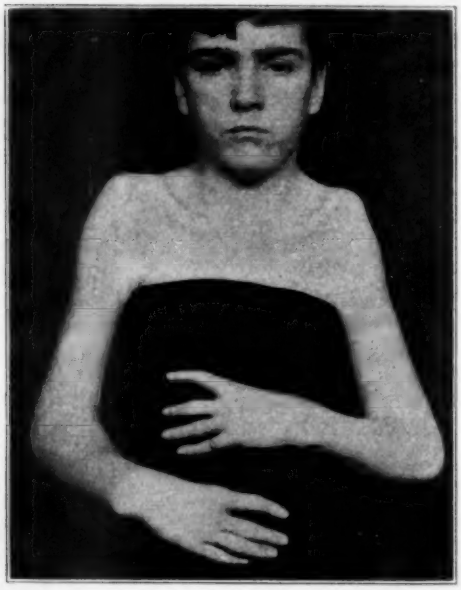

Fig. 4.—The patient as he appeared in May 1936.

Fig. 5.—Roentgenogram taken in May 1936, showing only four skeletal rays on each hand.

TREATMENT

The treatment of congenital dislocation of the shoulder falls into three types: (1) no therapy, (2) manipulative treatment and (3) operative treatment. Léniez [6] and Ranzi,[16] among others, offered their patients no treatment.

Whitman [17] advised manipulation of the shoulders similar to the manipulation of a congenitally dislocated hip; he concluded that a plaster bandage should be used to immobilize the reduced shoulder.

Cumston [2] reported excellent function following a simple open reduction, whereas Roberts,[18] Peckham [19] and Hitzrot,[4] obtained good functional results for at least five years after resection of the head of the humerus. Scudder [20] suggested three methods of attack: (1) wiring the head of the humerus to the glenoid cavity, almost effecting an arthrodesis of the joints: (2) excision of the head of the humerus, and (3) resection of the portion of the spine of the scapula obstructing motion.

The patient in the case reported here had three separate operations. The joint capsule was reefed on the right and the left shoulders in an attempt to overcome the dislocation by shortening the pendulous capsule. The humeri remained in place for the following three years. After Nicola's report in 1929 on the treatment of recurrent dislocation of the shoulder, the method he described was used on the right shoulder. These operations yielded satisfactory results in this case.

Congenital contracture of the joint was brought to the attention of the medical profession by Stern,[21] who in 1923 named the syndrome arthrogryposis multiplex congenita. He observed four cases. In one infant a congenital dislocation of the hip was also noted; in another there was subluxation of the tibia on the femur, but in no case was a dislocation of the shoulder present. There was extension contracture of the joints in his cases, which he believed to be caused by an incom-

16. Ranzi, E.: Ein Fall von doppelseitige (congenitaler) Schulterluxation nach rückwärts, Zentralbl. f. Chir. **39**:1144 (Oct.) 1904.

17. Whitman, R.: The Treatment of Congenital and Acquired Luxations at the Shoulder in Childhood, Ann. Surg. **42**:110-115 (July) 1905.

18. Roberts, J. B.: A Case of Excision of the Head of the Humerus for Congenital Subacromial Dislocation of the Humerus, Am. J. M. Sc. **130**:1001-1007 (Dec.) 1905; The Result Five Years After Excision of the Humeral Head for Congenital Subacronial Dislocation of the Humerus, Ann. Surg. **49**:431-432 (March) 1909.

19. Peckham, F. E.: A Case of Congenital Dislocation of the Shoulder Joint, Boston M. & S. J. **176**:355-356 (July) 1917.

20. Scudder, C. L.: Congenital Dislocation of the Shoulder-Joint, Am. J. M. Sc. **115**:125-131 (Feb.) 1898.

21. Stern, W. G.: Arthrogryposis Multiplex Congenita, J. A. M. A. **81**:1507-1510 (Nov. 3) 1923.

plete fibrous ankylosis of the joints. He considered this fibrous degeneration to be verified by the capsular thickening shown in the roentgenograms.

Stern, however, was not the first to describe this congenital anomaly. Wunsch [22] in 1901 presented a case under the term "multiple congenital contractures" and reviewed seven cases which had been reported prior to 1900. His reports include the cases of Zengerly, Schanz, J. Wolf, Bedner, Baumgartner, Redard and Wirt.

Since the eight cases reported by Wunsch in 1901, there have been at least twenty-one others recorded: four by Rocher [23] in 1918, five by Magnus in 1903,[24] 1928 and 1930, four by Sheldon [25] in 1932, three by Scarlini [26] in 1926, two by Lewin [27] in 1925, one each by Comby [28] and Price [29] in 1933 and one by Marconi [30] in 1922. At the orthopedic clinic in Iowa City nineteen cases of multiple congenital contractures have been seen since 1915.

The exact nature of this syndrome is still unknown. Price found changes in the spinal cord consisting of meningeal inflammation plus a lack of myelin in the anterior and posterior roots in a patient who came to autopsy. The muscle tissue showed partial degeneration, fibrous and fatty.

He expressed the belief that the degeneration of the cord and muscle proves that the condition cannot be a primary change in the joint, as Stern and previous authors emphasized.

Sheldon proposed the term "amyoplasia congenita" instead of the previous names used—multiple articular rigidity and arthrogryposis multiplex congenita. The name amyoplasia congenita does not describe the

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22. Wunsch, Max: Multiple congenitale Contracturen, Arch. f. Kinderh. **121**:161-178, 1901.

23. Rocher, H. L.: A propos d'un cas de luxation congénitale postérieure de l'épaule droite, Arch. de méd. d. enf. **21**:359-364 (July) 1918.

24. Magnus, F.: Ein Fall von multiplen congenitalen Contracturen mit Muskeldefecten, Ztschr. f. orthop. Chir. **11**:424-431, 1903.

25. Sheldon, W.: Amyoplasia Congenita (Multiple Congenital Articular Rigidity: Arthrogryposis Multiplex Congenita), Arch. Dis. Childhood **7**:117-136 (June) 1932.

26. Scarlini, G.: Sulle rigidita articolare congenita multiple e sul loro trattamento, Arch. di ortop. **42**:453-494, 1926.

27. Lewin, P.: Arthrogryposis Multiplex Congenita, J. Bone & Joint Surg. **7**:630-636 (July) 1925.

28. Comby, J.: L'amyoplasie congénitale ou rigidite articulaire multiple congénitale, Arch. de méd. d. enf. **36**:171-177 (March) 1933.

29. Price, D. S.: Case of Amyoplasia Congenita with Pathological Report, Arch. Dis. Childhood **8**:343-354 (Oct.) 1933.

30. Marconi, S.: Rigidita articolari congenite multiple, Arch. di orthop. **38**: 248-262, 1922.

most important feature of the anomaly—deficient motion of the joints. Since only one autopsy report (Price) is available at this date, the underlying pathologic changes are still a matter of conjecture.

There are no specific joints that are contracted in this congenital condition. All four limbs may be affected, as in Sheldon's case, or only the arms, as in Rocher's case and in the case reported here. The contracture may be either an extension (Stern) or a flexion (Scarlini) contracture.

In the case presented here there was limitation of motion in both elbows and wrists and in all the fingers. The absence of pronation and supination cannot be included in this syndrome since a bilateral radio-ulnar synostosis prevented this movement.

Althoug the contractures of the joints were not extreme, they were definite enough to preclude the possibility of the rigidity being within normal limits. As the rigidity of the joints had been present since birth, the diagnosis was limited to a congenital anomaly as the cause of the deformity.

Treatment for congenital articular rigidity varies. Scarlini successfully employed combined osteotomy and traction to correct the flexion deformity of the knee. He could not procure any increase of motion in the affected joints. Manipulation under anesthesia is of no value in decreasing the motion in the joints (Comby). Active and passive motion under skilled guidance in addition to reconstructive surgical measures seem to give the best results (Stern).

The radio-ulnar synostosis noted in this patient is not a very rare anomaly. Fahlstrom [31] collected one hundred and eighty-five reported cases in 1932. In some patients surgical intervention has been attempted with but little success (Blaine [32]). In most instances, as in this case, function is so little impaired as to discourage operative intervention.

The absence of thumbs or fingers is termed ectrodactylia or oligodactylia. The name ectrodactylia is also applied to fingers which are not entirely absent but are represented by small osseous nodules corresponding to the phalanges (Steindler [33]). Removal of these functionless appendages was performed in this case, although Kanavel [34] has not found operation necessary in his patients.

The bilateral seventh cervical ribs have given rise to no symptoms and therefore have not been treated.

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31. Fahlstrom, S.: Radio-Ulnar Synostosis: Historical Review and Case Report, J. Bone & Joint Surg. **14**:395-403 (April) 1932.

32. Blaine, E. S.: Congenital Radio-Ulnar Synostosis, with Report of a Case, Am. J. Surg. **8**:429-434 (Feb.) 1930.

33. Steindler, A.: Reconstructive Surgery of the Upper Extremity, New York, D. Appleton and Company, 1923, pp. 228-229.

34. Kanavel, A. B.: Congenital Malformations of the Hands, Arch. Surg. **25**: 1-53 (July); 282-320 (Aug.) 1932.

SUMMARY

A case is reported of a patient who presented several skeletal deformities, bilateral dislocation of the shoulders, congenital articular rigidity, congenital radio-ulnar synostoses, ectrodactylism and cervical ribs. Dislocation of both shoulders had been present since birth, but whether the dislocation was truly congenital is not certain. This case exemplifies the difficulty in ascertaining the causative factors in reported cases of congenital dislocations of the shoulders.

A review of the literature on some of the anomalous conditions is included.

HYPERPLASIA AND NEOPLASIA OF THE INTERSTITIAL CELLS OF THE TESTICLE

EDWARD E. JEMERIN, M.D.
NEW YORK

Considerable confusion exists as to the type and terminology of testicular tumors. Many varieties of tumor arise from the complex elements composing the testicle, and identities are further obscured by the possibility of teratoid origin. No attempt will be made to classify tumors of the testicle, but it may be stated that the scope of pure simple tumors of the testicle has been greatly narrowed by the study of teratoma testis and its derivatives. Ewing stated that all the common and nearly all the rarer testicular tumors arise from totipotent sex cells and that the monodermal forms represent one-sided developments of tridermal teratomas. Only rarely, he stated, do the stroma, duct cells, interstitial cells and adult seminiferous tubules give rise to characteristic growths. His view is more extreme than that of most, who separate from the group of teratoma testis and its derivatives the seminoma, or spermatocytoma, as being derived from adult seminal epithelium rather than from totipotent sex cells and also various rare tumor types supposedly derived from the supporting structures, which Ewing in large part includes in the teratoid group. From the major number of classifications, interstitial cell tumor, apparently because of its rarity, is omitted or given only passing mention.

Only isolated case reports of interstitial cell tumor are to be found in the literature. Even among these few, however, are found a number which are obviously spurious and others in which the description is too brief or the structural picture not sufficiently clear for a definite diagnosis to be established. Moreover, marked hyperplastic states of the interstitial cells have also been misinterpreted as actual new growths arising from these cells.

Though the primary concern of this paper is with tumors of the interstitial cells of the testicle, the rather more common hyperplasia of these cells will be dealt with first in order to avoid confusion between the two and to clarify the criteria on which a diagnosis of interstitial cell tumor may be based. The reported cases of interstitial cell tumor in human beings will then be critically reviewed. For completeness, hyperplasia and neoplasia of the interstitial cells as occurring in animals

From the Surgical Service of Dr. Harold Neuhof and the Department of Laboratories, Mount Sinai Hospital.

will be dealt with briefly. Finally, a report of a case of interstitial cell tumor occurring in the surgical service of Dr. Harold Neuhof, at the Mount Sinai Hospital, will be presented.

NORMAL HISTOLOGIC STRUCTURE AND OCCURRENCE OF THE INTERSTITIAL CELLS

The interstitial cells of the testicle (cells of Leydig) are modified connective tissue cells of epithelial contour lying in the testicular stroma between the seminiferous tubules. They vary considerably in number in different persons and in different periods of development. The cells are large and irregularly spherical or polyhedral; transition forms are common. The nuclei are relatively small and usually spherical and for the most part are situated eccentrically within the cells. They are pale and contain a sparse amount of chromatin and one or two nucleoli. Occasionally a cell has two nuclei. The characteristic feature of the cell is various inclusions in the abundant cytoplasm. In the fresh state the protoplasm is filled with highly refractile granules, a large part of which represent neutral fat or lipoids (cephalin, sometimes cholesterol esters). Numerous brownish granules of varying size having properties of waste pigment (lipofuchsin) are present. Other inclusions are droplets of colloid-like substance, granules of an indefinable nature and peculiar heavily staining rod-shaped crystalloids with rounded or pointed ends, known as Reincke's crystalloids (Maximow, Cowdry, Piersol and Kaufmann).

In the fetus interstitial cells are quite numerous. After birth they are reduced in number, being replaced by increased connective tissue. By the age of 8 very few are to be found. Until puberty the cells are not absolutely identical with those of the adult. From the time of puberty the cells increase in number and assume their characteristic appearance. Pigment does not appear until adulthood. At this time the cells are quite characteristic, are easier to differentiate and are collected in groups usually of four or five, though sometimes of as many as fifty. During adult life the cells decrease in number, so they frequently are hard to find and rarely even entirely disappear. Usually, however, though reduced, they are more numerous than prior to puberty. Finally, with old age, in the normal senile testis an inconstant increase in interstitial cells accompanies an increase in interstitial tissue, which occurs at the expense of the seminiferous tubules (Spangaro, Finotti and Kaufmann).

HYPERPLASIA OF INTERSTITIAL CELLS

Apart from normal variations in the number of interstitial cells, hyperplasia of varying degree is found in numerous disease and experimental states. At times the hyperplasia is so marked that the impression of beginning new growth is obtained. However, that this increase in

interstitial cells is secondary to the tubular atrophy which is invariably present will readily be seen from the nature of the material in which hyperplasia is observed.

Atrophic Senile Testes.—Spangaro described atrophic senile testes in contradistinction to normal senile testes. In the former the parenchymal atrophy is considerably more marked. He arbitrarily marked off three stages of atrophy on the basis of the degree of tubular degeneration, which progresses from cessation of spermatogenesis, to a decrease in the seminal cells, to a diminution in the caliber of the tubules with a thickening of their walls. Hyalinized connective tissue is laid down internal to the elastic layer of the tubular wall and increases progressively at the expense of this layer. The hyperplasia of the interstitial cells is marked and is present in a degree proportional to the stage of atrophy. The cells are grouped closely together in nests between and sometimes surrounding atrophic tubules. In three of fifty-two cases studied by Spangaro they formed nodes of from 0.5 to 1.8 mm. in diameter, which could be seen without the aid of a microscope. The cells are richer in pigment than the cells in the normal senile testes. Their death is marked by the appearance of vacuoles in the cell body. Of significance was the finding by Spangaro of apparent invasion of the atrophic tubules by the proliferating interstitial cells, which were observed in the walls of the tubules and occasionally even in their lumens. By elastic tissue stains he demonstrated that this invasion occurred only in cases of extreme atrophy when the elastic layer of the tubular wall was almost completely destroyed. What occurred, according to Spangaro, was not a true invasion but rather a consequence of the tremendous increase of interstitial cells which the altered tubules were not able to resist, the cells virtually growing into a wall that was already destroyed.

Chronic Illness.—In chronic illnesses in which cachexia is prominent, testicular atrophy and hyperplasia of the interstitial cells are features. According to Langhans, atrophy of the testicular tubules is quite common in tuberculosis and syphilis and less frequent in tumors of the testis. The characteristic change he described was a thickening of the connective tissue wall of the tubules, the thickened membrana propria showing an outer fibrous and an inner glistening homogeneous layer. The thickening at times led to obliteration of the tubular lumen. The interstitial stroma was broadened, and the blood vessels were injected. In some cases the interstitial cells were quite rich, sometimes near the rete and sometimes throughout the entire testis. In tumors of the testis hyperplasia of the interstitial cells was found in the portions of the testicle not involved by the new growth.

Hansemann also found this increase in interstitial cells in chronic cachectic conditions (tuberculosis, carcinoma, syphilis and pernicious

anemia) occurring even without involvement of the testis by the disease. Pigment was not always present in the cells. In a 44 year old man with pernicious anemia there was a marked increase in the Leydig cells. The testes were large, firm and gray-brown. The tubules could not be drawn out and were separated by broad strands of large pigmented interstitial cells. Similar changes were cited in a 50 year old man with chronic alcoholism and hemochromatosis of the intestines and the mesenteric lymph nodes.

Lubarsch reported an increase in interstitial cells in chronic phthisis and in the cachexia of carcinoma. He made the point that when the tuberculous process involves the testicle, the increase in the interstitial cells is not present in the tuberculous foci but in the remaining uninvolved portion of the testis.

Cordes studied the testes of thirty-one patients dying of chronic illnesses. There were fourteen who died of tuberculosis, mainly pulmonary, between the ages of 18 and 78. In seven there was a definite increase in the interstitial cells, with an absence of spermatogenesis, and in five of these pigment was present in the interstitial cells. Seven of the patients, from 30 to 63 years of age, died of a malignant growth, and in two there was an increase in the interstitial cells, with pigment present in the cytoplasm in one. Spermatogenesis was entirely absent in the testes of one of these patients and only occasionally seen in the testes of the other. In a 53 year old man dying of aneurysm of the aorta there was an increase of richly pigmented interstitial cells; also in a 68 year old man who died of chronic endocarditis. The testicles of seven of the nine remaining patients, consisting of four with chronic nephritis and five with a chronic cardiac condition or diabetes and varying in age from 28 to 92 years, showed active spermatogenesis. In none of these was an increase in interstitial cells noted.

Bouin and Ancel also noted an increase in the "interstitial gland" in chronic diseases (chronic pneumonia, generalized arteriosclerosis, renal sclerosis with cachexia, carcinoma and, particularly, phthisis). Regressive changes in the seminiferous tubules accompanied by progressive fibrotic processes in the interstitial tissue were noted by Simmonds to occur in chronic circulatory disease, arteriosclerosis, leprosy and syphilis. In any of these types of fibrosis he observed that there might be an increase in the interstitial cells.

Koch studied the testicles removed from three patients who died of generalized tuberculosis. In all he found a great increase in interstitial cells. In contrast, in local tuberculosis the interstitial cells were in the background. In the testicles of a 64 year old man with an inoperable carcinoma of the stomach and of a 56 year old man with generalized arteriosclerosis, myocarditis and emphysema, he found an absence of well preserved tubules and the presence of dense masses of pigmented

interstitial cells arranged in "liver-like formation." He found similar changes in the testicles of two patients with hepatic cirrhosis. In cases of diabetes mellitus in which there was some degree of cachexia these changes were present to a less marked degree. The testicles of six syphilitic persons were studied. In three an increase in interstitial cells was observed. These three patients, however, presented an additional systemic disease, hepatic cirrhosis, phthisis and a malignant growth, respectively. Koch concluded that the cachexia, with its accompanying tubular degeneration, was the essential and primary feature. Proliferation of the interstitial cells was secondary to the decreased pressure of the tissue resulting from parenchymal atrophy and would occur in all conditions in which there were severe changes in the tubules. Further tubular atrophy might then be caused by the pressure of the augmented interstitial tissue.

Hyperplasia of the interstitial cells in chronic cachectic states was discussed by Stoppato, with similar conclusions. Berblinger reported marked tubular atrophy and extreme proliferation of interstitial cells in a 26 year old underdeveloped man with tuberculosis of the lungs and lymph nodes and miliary tuberculosis. In a 61 year old man suffering from generalized severe arteriosclerosis and gout, a focal proliferation of interstitial cells was present around the remnants of the tubuli contorti. Finally, Kaufmann stated that in general diseases in which spermatogenesis decreases an increase in interstitial cells occurs.

Chronic Alcoholism.—Chronic alcoholism similarly leads to progressive alteration in the tubules of the testes, which frequently is accompanied by proliferation of the interstitial cells. Weichselbaum, and Weichselbaum and Kyrle reported fifty-seven cases of chronic alcoholism. The testes were all smaller than normal. Three stages of tubular atrophy were found: (1) cessation of spermatogenesis, (2) a decrease in the seminal cells and (3) diminution in the size of the seminiferous tubules, with thickening of the tubular wall and occasionally complete obliteration of the tubules. A widespread focal increase in interstitial cells was observed in all cases. They concluded that chronic alcoholism leads to changes in the tubules regardless of those present due to senility or to disease. However, their conclusions are not completely warranted, as thirty-three of the patients died of hepatic cirrhosis, two died of a combination of delirium tremens and hepatic cirrhosis and eight, though showing signs of chronic alcoholism (edema of the pia-arachnoid, fatty liver, etc.), died of carcinoma, apoplexy, encephalomalacia, chronic tuberculosis, pneumonia and leptomeningitis. Fourteen died of delirium tremens. It is apparent that except in the fourteen cases in which death was directly attributable to delirium tremens, the accompanying condition (hepatic cirrhosis, carcinoma, tuberculosis, etc.) might in itself

have been responsible for the hyperplasia of the interstitial cells. Another feature of interest noted was that the changes were greater in degree when cirrhosis of the liver complicated the chronic alcoholism than when other chronic diseases were present concomitantly.

Hansemann, Berblinger and Kaufmann also noted tubular atrophy and hyperplasia of the interstitial cells in the testes of persons with chronic alcoholism.

Acute Illnesses.—In the realm of acute illnesses, Cordes reported the changes in the testes of thirty-six patients. Twenty between the ages of 24 and 59 died of pneumonia. In thirteen of these there was an increase in interstitial cells. Spermatogenesis was absent in seven and sparse in three of the thirteen. Five patients between 26 and 58 died of typhoid. All showed an increase in the interstitial cells. Spermatogenesis was absent in three and only rarely seen in one. The testes of a 19 year old youth dying of tetanus also showed an increase of interstitial cells. Spermatogenesis was absent and the interstitial cells augmented in a case of polyarthritis. In the remainder, including cases of scarlatina, sepsis, peritonitis and meningitis, there were preservation of spermatogenesis and no hyperplasia of the interstitial cells. Lastly, in six patients dying accidentally there were no increase in the interstitial cells and preservation of spermatogenesis in all.

Bouin and Ancel mentioned the occurrence of hypertrophy of the "interstitial gland" in persons with illnesses running a rapid course, such as pneumonia and certain forms of tuberculosis.

In an investigation of the testes of fifty-eight persons dying of acute illnesses of various sorts, Kyrle observed a proliferation of interstitial cells in all that showed marked parenchymal alteration. He concluded that the factor determining the occurrence of hyperplasia of the interstitial cells was an injury to the parenchyma sufficiently intensive or long lasting to produce at least cessation of spermatogenesis.

Undescended Testes.—When the testis remains undescended, its function is not usually preserved. As a rule it undergoes early atrophy with narrowing, sclerosis and atrophy of the tubules. In light of the data already presented, one should expect to find hyperplasia of the interstitial cells not uncommon.

Finotti reported sixteen cases of undescended testes. Atrophy was constant. All the testes were smaller than normal, with the exception of one, and the size of this was retained merely by virtue of exceedingly marked hyperplasia of the interstitial cells. Varying degrees of tubular atrophy, which was sometimes quite conspicuous, was present in all cases. The increase in the interstitial cells was constant. The cells were found singly, in groups and in rows between the atrophic tubules. The nuclei were relatively small. The cytoplasm contained fat, pigment and occa-

sionally Reincke's crystalloids. In two cases the proliferation was extreme, with the cells in compact round masses traversed by numerous capillaries. The nuclei were always well preserved. Cells with two nuclei were not uncommon. Rarely, metaplasia (anaplasia) was seen. The intense proliferation and the masses of young cells with numerous blood vessels gave Finotti the impression of a proliferation like that of a beginning new growth. Invasion of the atrophic tubules by the interstitial cells was never observed.

Félizet and Branca, in their researches on ectopic testicles removed at and after puberty, made similar observations. Before puberty, interstitial cells were rare. However, in ectopic testicles removed after puberty, they found atrophy of the seminiferous tubules accompanied by an increase of the interstitial cells between the tubules to be the rule. The tubules showed varying degrees of atrophy and sclerosis, with the seminal lineage practically never complete. Interstitial cells were almost always increased in number. At times they replaced practically the entire stroma. They contained pigment, fat vacuoles and Reincke's crystalloids. Their topography was not fixed. They occurred individually, in islands, as rounded nodules, as cords between the tubules or as girdles around them. Their aspect was often epithelioid. Occasionally, they were seen in the walls of the tubules. This the authors interpreted as indicating an evolution in situ of the interstitial cells from the connective tissue of the tubular wall. (Compare this explanation with that of Spangaro.)

Grynfeldt, Truc and Guibert reported a case of ectopic testicle in which there was considerable hyperplasia of the "interstitial gland."

Grynfeldt, Truc and Guibert's Case.—A 56 year old man underwent a suprapubic cystostomy for symptoms of prostatism. At operation a small soft testicle was found 2 cm. above the pubis and was removed. The other testicle was descended. Microscopically, the tubules of the removed testicle were seen to be profoundly modified. The epithelial lining was almost completely atrophied, and spermatogenesis was absent. The tubular walls were sclerosed, with enormous development of the collagenous coat. The tubular lumens were narrowed. Considerable collections of well vascularized chromophilic masses infiltrated the intertubular stroma, forming cords which insinuated themselves in the intertubular spaces, broad ridges which pushed the tubules back, and perivascular and peritubular collars. These collections were formed of cells identified with interstitial cells. The cells were polygonal, with round or oval nuclei containing one or two nucleoli. The cytoplasm was acidophilic and usually homogeneous, though occasionally it was granular. With higher magnification, the cytoplasm was seen to be hollowed by vacuoles of varying dimension, which at times filled the entire cell and gave it a foamy appearance. No Reincke's crystalloids were present, but a number of cells showed black granules when stained with iron hematoxylin. Large cells with multilobed nuclei or nuclei in amitotic division were seen. Actual mitoses were rare. Occasionally there were seen cells "invading" the tubular walls.

The authors expressed the belief that the amitoses, the nuclear monstrosities and the tubular "invasion" were indications of a possible precancerous growth. However, the observations of Spangaro of interstitial cells in the walls of the tubules in the hyperplasia of interstitial cells occurring in atrophic senile testes and those of Félizet and Branca in cryptorchidism hardly permit the finding of these cells in the tubular walls in hyperplastic states to be used as evidence of a precancerous state. Amitoses and nuclear monstrosities have also been observed previously in the more vigorous hyperplasias.

Pick, Simmonds, Koch, Kyrle and Stoppato also noted the frequent finding of marked hyperplasia of the interstitial cells accompanying the tubular degeneration occurring in undescended testes.

Pseudohermaphroditism.—Similarly, one would expect to find hyperplasia of the interstitial cells in pseudohermaphrodites in whom the testicular function is diminished or absent. The literature contains reports by Stroebe, Pick and de Josselin de Jong.

Stroebe's Case.—A 63 year old man who died of esophageal carcinoma presented external genitalia of normal appearance. The penis appeared normal, measuring 10.5 cm., and the urethral orifice was in the proper position. The scrotum was well developed, but there were no testes palpable. In the abdomen was found an elongated uterus with well developed round ligaments and tubes. On either side was a bean-shaped, grayish red organ which microscopically were seen to be testes. Each was enclosed in an albuginea. The tubules were degenerated and largely hyalinized, with their epithelium practically gone. The tubular lumens were considerably narrowed. The tubules were embedded in a richly developed interstitial substance containing numerous full blood vessels and consisting in the main of large polymorphous cells with round, oval or occasional spindle-shaped nuclei and well developed protoplasm containing fine brown-yellow pigment. This interstitial tissue surrounded the tubules or groups of them in bands of varying width. Many of the collections were sufficiently large to be visible macroscopically as islands of pigment cells the size of a pinhead.

Pick's Case.—A 38 year old "internal masculine pseudohermaphrodite" had atrophic testes, measuring 3.5 by 2 cm. The decrease in size was due to parenchymal atrophy. The markedly diminished tubules were embedded in, and largely overgrown by, a stroma containing groups, strands, nodules or regular diffuse sheets of interstitial cells which at times formed the only intertubular stroma. These cells were of epithelioid appearance, with vesicular nuclei and intensely pigmented cytoplasm. At times the cytoplasm contained vacuoles of varying size. Mitosis were not seen, despite the vigorous proliferation. No Reincke's crystalloids were present. The largest groups of cells measured about 1 mm. and were visible grossly.

De Josselin de Jong's Case.—A 42 year old "internal masculine pseudohermaphrodite" presented a large tumor in the left testicle. The right testicle was situated at the external inguinal ring and was reduced to the size of an acorn. Microscopically, the tubules were seen to be badly developed; spermatogenesis was absent. The intertubular stroma was increased and contained groups of inter-

stitial cells. For the most part these groups were small, though one of them measured 2.5 mm. and was visible grossly. The details of this case with reference to the left testicle will be given later.

Local Conditions.—Hyperplasia of the interstitial cells of varying degree has been observed in various local conditions, such as long lasting compression of the cord, stricture of the vas, deferentitis and chronic disease of the bladder and prostate (Simmonds).

Experimental States.—In experimental states causing tubular atrophy, hyperplasia of the interstitial cells is also frequently noted. Kyrle subjected the testes of thirty-five dogs to roentgen irradiation. The exposure given to thirty-three was not sufficient to cause more than minimal changes. The testes were slightly reduced in size. The tubules were smaller, and the membrana propria was thrown in fine folds. The interstitial tissue was moderately proliferated. Two animals showed a more abnormal reaction. Their testes were reduced to one-half normal size. Microscopically, this was seen to be due to extreme atrophy of the tubules, which were much thickened and sometimes hyalinized. The interstitial substance was much increased, largely by virtue of an increase in the interstitial cells. Biopsy specimens were taken from one of these dogs after each of three successive exposures. A greater degree of parenchymal atrophy and of proliferation of interstitial cells was found with each successive exposure. Simmonds similarly noted atrophy of the specific elements followed by proliferation of the interstitial cells in testes that had been subjected to irradiation. Both authors observed that when the toxic effect of the roentgen rays was withdrawn, if atrophy of the parenchyma had not progressed too far, regeneration of the epithelium followed by a regression of the interstitial cells occurred. The authors concluded that the hyperplasia observed was secondary to, and compensatory for, the parenchymal destruction.

Experimental atrophy produced in different fashion by Bouin and Ancel resulted in identical changes. They observed that after the ligation of the vas in young rabbits the seminal tubules were poor in cells and contained no spermatozoa, even after four months, while the interstitial cells were well preserved and somewhat augmented. When ligation of the vas was accompanied by contralateral castration, after six months the testes were definitely smaller and the seminiferous tubules showed only a few spermatogonia, while the Sertoli cells were unchanged and the "interstitial gland" enormously developed. In from ten to twelve months the tubules were very shriveled, the Sertoli cells were degenerated and the testes consisted almost entirely of hyperplastic Leydig cells. The authors also induced states of chronic alcoholic and of chronic tuberculous intoxication in rats, with resultant hypertrophy of the "interstitial gland." Bleeding of rats or destruction of the adrenal capsule had the same effect.

Summary.—It is seen, then, that in any condition, local, general or experimental, in which cessation of spermatogenic activity and tubular atrophy occur, hyperplasia of the interstitial cells may secondarily ensue. This secondary hyperplasia may be so marked as to form almost the entire stroma and even to maintain the size of the testicle despite marked tubular atrophy. Further tubular atrophy may be caused by pressure of the greatly augmented interstitial cells. The primary and initiating factor, however, is the parenchymal destruction. At times the appearance of beginning new growth is suggested by the more vigorous hyperplasia, with marked tubular atrophy, anaplasia, bizarre nuclear forms and even apparent invasion of the tubular wall. It is to be remembered in this connection that all these features also accompany the less vigorous hyperplasia in which no question of possible new growth exists and hence in themselves cannot be used as criteria to distinguish one from the other. Moreover, in practically all cases the proliferation can be seen to be intertubular, involving the entire testicle diffusely and uniformly rather than seeming to originate from a single focus and expanding centrifugally from there, as one would expect to see in the case of new growth. The proliferating cells retain for the most part the characteristics of the mother cell. They are polymorphic cells with abundant acidophilic cytoplasm and relatively small nuclei. Various inclusions (lipoid droplets, pigment, refractile granules, etc.) may be observed in the cytoplasm, though these changes are not constant.

TUMORS ARISING FROM THE INTERSTITIAL CELLS

The first reference to tumors derived from interstitial cells was made by Waldeyer in 1872. He spoke of tumor formations arising from the perithelial cells in the brain, lymph vessels and testes, forming soft neoplasms consisting of vascular plexuses, the individual vessels of which had a covering of epithelial cells which assumed the arrangement of anastomosing strands. The individual cells he described as being rich in protoplasm, containing fine dark granules and having pseudopods. He identified these with Leydig's cells. To this type of lesion he gave the name plexiform angiosarcoma. He specified that in the testis such a growth might readily be confused with carcinoma.

Hansemann in 1895 next referred to tumors which he believed to arise from the cells of Leydig. Practically no description of the component cell is given, except that the tumors described were composed of large cells surrounded by a netlike intercellular substance, the cells markedly resembling interstitial cells. Such growths, he said, might resemble a sarcoma or a carcinoma. An illustration is provided.

Later authors who interested themselves in the subject of interstitial cell tumor seem to be agreed that the tumors described by Waldeyer and Hansemann are not to be included in this category. Hansemann himself,

in discussing Waldeyer's plexiform angiosarcoma, stated that the description was doubtless too far reaching and would probably include both angiosarcoma and interstitial cell tumor, Waldeyer having been misled into including interstitial cell tumor in this classification because of the intimate relation of the tumor cells to the vessels. And, he added, there is no real surety that Waldeyer observed actual interstitial cell growths, as the relation of the vessels was closer than would be present in growths of this type. Langhans similarly was unable to accept Waldeyer's conclusions. Krompecher identified the tumors described by Hansemann with his group of large cell alveolar sarcomas (really carcinomas), and Debarnardi was in accord with this view. Chevassu, in his treatise on testicular tumors, in which he described both the seminoma and the interstitial cell tumor, stated that the growths described by Waldeyer as plexiform angiosarcomas were probably seminomas, and that although Hansemann's description was summary, the illustration in the text left little doubt that he likewise was dealing with seminomas. The cellular constituents of the lesions described by Hansemann, he stated, were not like those of interstitial cells. The nuclei were larger and the cytoplasm less abundant, with an absence of inclusions. Ewing stated that the descriptions of Waldeyer and of Hansemann were brief, suggesting the possibility of interstitial cell tumor but hardly establishing the fact. He referred to certain cases of his own in which portions of the tumors resembled Hansemann's tumor but the growths were diffuse carcinomas occurring as part of teratoid growths. Masson and Sencert, who later reported a case of interstitial cell tumor, were in accord with the opinion that the tumors referred to in reality arose from cells of the seminal line. Panà similarly concurred, and Peyron criticized the classification of these growths as interstitial cell tumors as errors in diagnosis.

In 1906 Chevassu described the seminoma and identified Waldeyer's plexiform angiosarcoma and Hansemann's interstitial cell sarcoma with it. He then described a tumor with characteristics isolating it from all other testicular growths. It was composed of cells resembling markedly the cells of Leydig and different than those of the common round or polygonal cell tumor.

CHEVASSU'S CASE.—A 27 year old man, with his left testicle in the inguinal canal, several years previously had been operated on for hernia on that side, and in the ensuing months a tumor had appeared under the scar. This had gradually enlarged to the size of a fist. The mass was removed at a second operation and was found to contain the left testicle, which was enlarged to the size of a small hen's egg. The tumor was quite hard and had apparently completely replaced the testicle. No trace of normal testicle was apparent on section. The sectioned surface was seen to consist of reddish yellow lobules divided off by paler spans of what proved to be connective tissue. Microscopically, the reddish yellow lobules

were composed of masses of large polygonal cells with voluminous, deeply tinted cytoplasm containing deeply staining granules and numerous vacuoles, which at times riddled the cytoplasm. No Reincke's crystalloids were seen. The nuclei were spherical and clear and in general compressed toward one border of the cell. Traversing the cellular masses were adult capillaries, frequently in close contact with the tumor cells. The entire tumor was limited by a shell of fibrous tissue in which were found a few flattened, thickened, sclerosed, residual seminiferous tubules. Histologically, the lesion seemed benign, and twenty-two months after operation the patient was alive and well with no evidence of recurrence.

This tumor, according to Chevassu, was a neoplasm of the primitive interstitial cells, the first to be described. The similarity of these cells to interstitial cells, with their voluminous, highly staining cytoplasm, containing deeply staining granules and vacuoles, their small clear nuclei and their frequent close contact with capillaries, was as apparent as their dissimilarity to the cells of tumors derived from seminal epithelium. The absence of Reincke's crystalloids and other secretory products he deemed of no importance. The rapidity of proliferation did not furnish sufficient time for the edification of these products. Authors studying the problem of interstitial cell tumor since have all accredited the authenticity of this tumor's origin from interstitial cells.

Kaufmann, the following year, described the testes removed from a 30 year old man, both of which were the seat of similar changes, and in 1908 he reported on the testicle removed from the brother of this patient, a man of 34.

KAUFMANN'S CASE 1.—The patient was mentally retarded, though strong physically. Both testes were in the scrotum and presented similar changes. One measured 9 by 6 cm., and the other was slightly smaller. The shape of the testicles was retained. The consistency was firm, with a grating on sectioning. Grossly, the tumor was broken into irregular, plump, brownish red lobules by connective tissue. Microscopically, the parenchyma was reduced to a few scattered subalbugineal groups of atrophied tubules. Proliferation of the interstitial cells, such as is ordinarily found in cases of diffuse hyperplasia, was absent from between these subalbugineal tubules, which appeared as though pushed outward by the developing tumor mass within. The tumor tissue consisted of netlike strands, nests and masses of large epithelioid cells in intimate relationship to fine vessels which subdivided the large cell masses. The arrangement and cell type were very suggestive of liver, adrenal cortex or alveolar tumor of the carotid gland. The individual cells were polymorphous, mostly polyhedral. The nuclei were round or elliptic and about the size of a red blood cell, though some were twice as large. The network of chromatin was sparse. One or two nucleoli were present. Occasionally multinucleated cells were seen. The protoplasm was granular, with many vacuoles. Many cells contained fine round, yellow brown pigment granules, while others seemed diffusely pigmented. The pigment was similar in nature to that occurring physiologically in interstitial cells. The fat content of the cells was rich, as evidenced by the presence of numerous large and small droplets without destruction of the cell. This gave the cells a weblike appearance on extraction of the fat. Reincke's crystalloids were not seen.

KAUFMANN'S CASE 2.—The testicle of the brother of the preceding patient was fully descended, weighed 150 Gm., and was 9 cm. long. Macroscopically and microscopically, it was similar in all respects to the brother's, except that the tubular crests were lacking. The other testicle in this patient, which was left in situ, was voluminous and quite likely, Kaufmann stated, the seat of similar changes.

Kaufmann stated that the growths were probably benign, because, though present for many years, there had been no invasion of the tunica or epididymis. However, he did not make a definite statement, because he considered the polymorphism of the cells to be suggestive of a malignant process.

The character of the cells in these cases is obviously fundamentally similar to that of the cells of Leydig. Chevassu, who had an opportunity to study the material in Kaufmann's cases, found the cells quite like those in his own. The appearance of the cells and of their protoplasm and nuclei were, he stated, similar in all specimens examined.

Dürck, in the same year, described four cases in which there was an enormous increase in interstitial cells.

DÜRCK'S CASE 1.—A vigorous 25 year old carpenter died of a fractured skull sustained in a fall from a building. Both testes were in the scrotum but were remarkably small, measuring 1.8 by 1 cm. and weighing 7 Gm. with the epididymis. Their color was dark brown. The tubules were extraordinarily reduced, their tunica propria thickened and hyalinized, their lumens narrowed and their epithelium atrophic, with barely a sign of spermatogenesis. Between the atrophic tubules were seen broad beds of large polygonal cells with abundant cytoplasm and round vesicular nuclei with definite nucleoli. These cells made up the bulk of the testicle.

DÜRCK'S CASE 2.—A 64 year old man died of purpura.. The testes, which were brown and about the size of a hazelnut, were in the peritoneal cavity. The tubules were again seen to be reduced in number, their walls thickened with concentric layers of fibrous tissue and their lumens reduced, with few epithelial cells. The interstitial cells between the tubules were greatly increased and large, their nuclei being variable in size and the nucleoli large and dark. The cytoplasm contained abundant sharply refractile fat vacuoles and abundant, though irregularly distributed, light brown pigment.

According to Dürck, the picture presented was suggestive of polymorphous pigment cell sarcoma.

DÜRCK'S CASE 3.—A powerfully built man of 45, who died suddenly of a heart attack, was found to have aortitis and disease of the coronary artery at postmortem examination. Both testes were in the scrotum and were small and dark. The seminiferous tubules were reduced in number and size, and their tunica propria was thickened and hyalinized. The major portion of the preparation was composed of intertubular masses of interstitial cells rich in fat vacuoles and in irregularly arranged pigment.

DÜRCK'S CASE 4.—A 43 year old man, who died of tuberculous pachymeningitis, had contracted gonorrhea thirteen years prior to his death. Two years later he received a heavy blow on the scrotum, after which the left testicle diminished in size, while the right became larger for a time and then remained

constant. The right testicle was larger than a walnut. The seminiferous tubules had almost entirely disappeared. Only occasionally was a small calibered tubule lined by a single layer of epithelium seen. Practically the entire preparation consisted of cell-poor bridges of fibrillary tissue with the intervening spaces entirely filled by polygonal cells with vesicular nuclei. The cells in this case were somewhat smaller than those in case 1. Atypical mitoses were present.

To Dürck, the picture resembled that of a sarcoma. The left testicle was the seat of a diffuse fibrous orchitis in which interstitial cells were not seen.

Dürck was of the opinion that in his cases the tumors were of a special form, even though the testes were smaller than normal. Evidence for their neoplastic nature, he said, is seen in the fat degeneration in case 3, in the pigmentation in cases 2 and 3 and in the variability of cell form and the atypical mitoses in case 4. The proliferation of the interstitial cells was primary, he added, and the tubular atrophy secondary. This might occur in descended as well as in ectopic testes. In cases 1 and 3, there was no etiologic factor that might produce primary tubular atrophy.

On analysis of the material presented, one sees that the picture found is much more closely akin to hyperplasia than to neoplasia. Except in case 4, the testes were all considerably smaller than normal. Though reduced in number, tubules were present throughout the testes in the first three cases, with proliferation of the interstitial cells being essentially intertubular, rather than pushed back to the subalbugineal region by an expanding lesion. This is the topography seen in cases of hyperplasia as compared to that seen in Kaufmann's cases, in one of which no tubules were present, while in the others they were limited to a few subalbugineal groups with no interstitial cells between them, or as compared to that in Chevassu's case in which only a few tubules were found in the limiting fibrous shell. The fat and pigment found were, of course, cytoplasmic inclusions, which are normally present. The variability of cell form and the atypical mitoses have been seen in the more vigorous hyperplasias described. In case 2 an etiologic factor for primary tubular atrophy and secondary hyperplasia of the interstitial cells was present, namely, cryptorchidism. In cases 1 and 3 there was no apparent etiologic factor for the parenchymal atrophy. In case 4 death was due to tuberculous pachymeningitis. Whether tuberculosis was present in the other organs is not stated. Cachexia due to tuberculosis as well as testicular atrophy due to gonorrhea are agents which can produce secondary hyperplasia of the interstitial cells. However, the testicular injury with its immediate sequel of testicular alteration is also of interest because of the alleged relationship of injury to testicular tumor. Moreover, the growth in this case, by its gross and microscopic characteristics, more

closely approaches an actual neoplasm. It was larger than the growths in the other cases, being almost the size of a normal testicle. The tubules for the most part had disappeared. The cells were less typical, and it is in this case that the atypical mitoses were seen. The question of neoplasm in this case must therefore remain sub judice.

Thus there remains one case of questionable neoplasia of the interstitial cells. The conditions in the other three cases can hardly be designated as anything but hyperplasia, though because of the absence of any evident etiologic factor for the primary tubular atrophy in cases 1 and 3 the possibility that hyperplasia of the interstitial cells may arise as a disease sui generis must be kept in mind. Also, as suggested by Peyron, one must consider that the presence of a hyperplasia of these cells may serve as a soil for the development of an actual neoplasm.

The next report is that of Stoppato, who in 1911 described three growths which he designated as interstitial cell tumors.

Stoppato's Case 1.—A 38 year old man had a testicular tumor which developed painlessly over the course of a year. It measured 8 by 6.5 by 2 cm., and was grayish with a central yellow area of softening. No normal parenchyma was left, though beneath the albuginea were the remains of some seminal tubules, with thick, hyaline walls. The tumor tissue was composed of cell strands of from two or three to twenty or thirty cells in width separated by a fibrous stroma containing a few small cells. The tumor cells were large (from 14 to 18 microns), round or polygonal. The protoplasm stained violet-rose with hematoxylin and eosin, was irregularly granular and contained numerous vacuoles, giving the cells a foamy appearance. The nuclei were also large (from 8 to 14 microns), rich in chromatin and round, polygonal or oval, with at least one nucleolus. Mitoses were seen. Necrotic areas were present. The cells contained no pigment or crystalloids, but the protoplasm was rich in glycogen. Peripherally, between the residual tubules, were seen groups of from three or four to thirty or forty true interstitial cells. They differed from the tumor cells in that they were relatively rich in protoplasm, their nuclei were vesicular with little chromatin, the nucleolus was more sharply defined and the protoplasm was free from glycogen. Transitional forms to cells with nuclei richer in chromatin were observed. However, these transitional forms still were free from glycogen and showed no mitotic figures.

Stoppato's Case 2.—A 26 year old man, whose clinical history was not available, had a testicle which measured 9 by 6 by 4 cm., was grayish red and elastic and was divided into prominent lobules. The only trace of testicular tissue present was some atrophic tubules beneath the albuginea. The tumor cells were arranged in strands separated by an interweaving cell-poor stroma, which was richer in cells than that in case 1, the cells being mainly lymphocytes. The tumor cells were large (from 13 to 15 microns). The protoplasm was relatively sparse, clear and vacuolated. The nuclei were also large (from 9 to 12 microns), with scanty chromatin, and usually contained one nucleolus. Mitoses were observed. No pigment, crystals or crystalloids were seen. Again the cells were rich in glycogen. Between the atrophic tubules were groups of true interstitial cells—large polyhedral cells with abundant rose colored cytoplasm lacking glycogen and eccentric vesicular nuclei.

STOPPATO'S CASE 3.—A tumor occurred in a fully descended testicle that had undergone tumefaction after an injury suffered two months previously. It was firm, measured 8 by 5 by 3.5 cm. and showed a lobular structure on cut section. It was gray or grayish red. An occasional atrophic seminiferous tubule was seen beneath the albuginea. Apart from this no trace of testicular parenchyma remained, the tumor consisting of cellular tissue divided into strands by a cell-poor stroma. The tumor cells were large (from 14 to 18 microns), and the protoplasm pale red, finely granular or water clear. The nuclei were large (from 8 to 12 microns) and rich in chromatin and contained from two to four nucleoli. Mitoses were observed. The cytoplasm contained no pigment, crystals or crystalloids, though much glycogen was present. In this case no normal interstitial cells were seen between the atrophic seminiferous tubules beneath the albuginea.

The cell type found in these three tumors differs both from that found in the cases reported by Kaufmann and Chevassu and from the interstitial cell. The cytoplasm was scanty, without inclusions of any sort, and contained much glycogen. The nucleus was large, filled the greater portion of the cell and was rich in chromatin. Moreover, in the first two cases real interstitial cells were observed between the residual tubules, these cells differing markedly from the actual tumor cells. Stoppato himself, in analyzing his cases and comparing them with those of Chevassu and Kaufmann, admitted that differences existed and that the resemblance of the cells of his cases to interstitial cells was not as great as that of the cells in the cases of the two aforementioned authors. That his concept of the nature of the lesion he observed was not quite clear is further evidenced by the fact that he included in his discussion the cases of Waldeyer and Hansemann as cases of true interstitial cell tumor. He stated further that by using Debernardi's classification his cases would fall into the group of large cell malignant tumors, though they were not absolutely identical with them. It has been shown that this group of tumors is derived from spermatogonia (seminomas).

Doubtless the growths in these three cases are to be classified as large cell testicular tumors or seminomas rather than as neoplasma derived from the interstitial cells. Further support is given this view by Frank, who allied Stoppato's material with large cell testicular tumors derived from the layer of spermatogonia of the tubuli contorti. Ewing's description of embryonal cell carcinoma of the testicle is practically identical with the appearance of these growths. He described under this heading lesions composed of large round or polyhedral cells, rich in glycogen with hyperchromatic nuclei. The stroma, similar to that in Stoppato's cases, was scanty, or strands of lymphoid tissue might be prominent. Finally, Peyron stated, after having had the opportunity to study Stoppato's original preparations (which were placed at his disposal by Professor Wegelin, associated with the same institute as Stoppato), that the tumors reported were seminomas. The view held by Professor Wegelin, Peyron added, was in accord with his.

PEPPERE'S CASE (1922).—An ovoid, encapsulated, soft, yellow tumor of the testicle, the size of a hen's egg, was removed from a 1½ year old child. The tumor had grown slowly from birth. No seminal tissue was seen. The neoplastic tissue was uniform and was composed of cells with uniform morphologic characteristics. The cells were compressed like "tile paving" and were interrupted solely by turgid capillaries. The individual cells were polyhedral or polygonal, with abundant clear cytoplasm. The nuclei were large and vesicular, with sparse chromatin filaments.

Peppere's interpretation was that the lesion was a sarcoma derived from the cells of Leydig analogous to the hypertrophy that occurs in cryptorchidism. Though the description given is too summary for definite conclusions, it leaves the impression that the component cell is more closely allied to that of Debernardi's large cell tumors (seminoma of Chevassu or embryonal carcinoma of Ewing).

The next contribution was made by Masson and Sencert in 1923.

MASSON AND SENCERT'S CASE.—A 52 year old mason, with an irrelevant previous history, had his right testicle removed for a heavy swelling of several months' duration. The tumor was hard, grayish with blue areas and quite vascular. It measured 8 by 4 by 4 cm. and was completely enclosed by the albuginea. Atrophic, compressed, thickened seminiferous tubules were present in the subalbugineal region, apparently pushed toward the periphery by a tumor arising in the depths of the testicle and expanding outward. Separating the tumor from the subalbugineal parenchyma was an imperfect fibrous capsule without precise limits, invaded and dissociated in areas by neoplastic tissue. A rare interstitial cell was found between the tubules immediately under the albuginea. The tumor tissue was formed of interlacing, anastomosing cellular cords of irregular thickness, enveloped by a fine connective tissue sheath in which were numerous capillaries. The arrangement resembled the crescents of the seromucous salivary glands. Centrally the tumor was necrotic and hemorrhagic. The tumor cells were large and polymorphous and intensely though unequally acidophilic, some being colored *en masse* and others finely granulated by eosin. Some cells were vacuolated and some were practically excavated. Still others were strewn with highly colored refractile granules similar to secretory granules. The nuclei were round or oval, voluminous, and central or eccentric and were always situated in a dense cytoplasmic region. They contained fine chromatin granules and one or two nucleoli. Mitoses were observed, ordinary and pluripolar.

Four years later the patient returned with a metastatic mass in the right groin. He died of bronchopneumonia twenty-six days after extirpation was attempted. At autopsy there were found in addition to the large recurrent mass in the right groin, which had penetrated the femur, numerous metastases in the lungs and a large metastatic gland at the root of the aorta. The metastatic tumors were reddish, partially hemorrhagic and spotted with yellow necrotic areas. Microscopically, all were identical. Where not necrotic, they were compact and exceedingly vascular. The cells formed mosaics with innumerable capillaries. The appearance was similar to liver or to adrenal cortex. The tumor cells when dissociated were spherical. Most contained minute grease drops in the periphery; some were quite loaded with fat. A few cells had feeble amounts of glycogen, but never in abundance—different, according to the author, than in the seminoma.

The cytoplasm was acidophilic and granular, and the nuclei were spherical. In the palisade cells along the sinusoidal vessels the nuclei were always on the far side. The nuclear texture was finely reticulated. One or two nucleoli were present in each cell, and mitotic figures were numerous. These cells, Masson stated, differed more from interstitial cells than those of the original tumor; so much so, that their nature would be difficult to affirm without study of the original tumor. He stressed the resemblance of the picture presented in these metastatic foci to that of an endocrine gland.

The resemblance of the cells composing this tumor to interstitial cells is striking despite the absence of pigment or crystalloids. This absence has already been encountered in Chevassu's case. Although the lack of this very characteristic feature of interstitial cells makes it difficult to state with complete assurance that this tumor originated from these cells, the polymorphism of the cells, with their abundant, highly colored cytoplasm containing lipoid and highly refractile secretory granules, makes this quite likely. Cells derived from epithelial lineage lack the size and marked colorability of the cytoplasm of these cells. The arrangement of cells to resemble liver or salivary gland has also been seen in previous cases. Oberndorfer, Panà, Caudière and Peyron apparently all agree as to the derivation of this neoplasm from the cells of Leydig. The obvious malignant nature of the growth segregates it somewhat from those reported by Kaufmann and Chevassu but certainly does not militate against its interstitial cell origin.

De Josselin de Jong's Case (1926).—An intra-abdominal tumor the size of a child's head was found arising from the left intra-abdominal testicle of a 42 year old "internal masculine pseudohermaphrodite." On section, the tumor was in most places soft, bloody and necrotic. The small, well preserved areas were gray-yellow or brownish. Microscopically, the greater portion was amorphous, edematous and somewhat bloody, with granular masses showing strong necrosis. Small islands of fairly well preserved cells were seen, though the cells themselves showed many signs of degeneration (fat droplets, vacuoles and hydropic swelling). This gave the tumor an irregular structure. The cells were often grouped to form a netlike arrangement of strands. At the edge of the growth was a connective tissue stroma in which the tumor cells lay in bands, rows or irregular groups. The cells were better preserved here and were polymorphous. The protoplasm was variable, and in some cells abundant and somewhat granular, with large or small vacuoles. The nuclei were of variable size, mainly round, staining clearly. With sudan III many of the vacuoles in the protoplasm were seen to be fat globules. The author stated that in many areas the cells resembled interstitial cells. The tumor was rich in blood vessels, which were thin walled, consisting of only one layer of endothelial cells. The tumor cells seemed to cling to the blood vessels or were limited by them. No pigment or crystalloids were found. No mitotic figures were present. The growth was malignant. De Jong received a communication from the patient's physician that metastases had developed but that the patient was now visiting some faith healer for treatment. The tubular atrophy and hyperplasia of the interstitial cells in the right testicle have already been described.

In this tumor degenerative processes were so active and prominent that it is difficult to draw any positive conclusions as to its genesis. The author expressed the belief that the growth was a malignant tumor of sarcomatous nature arising from the interstitial cells of the testicle. He discussed the possibility of malignant hypernephroma but dismissed it because of the hemorrhagic nature, the widespread necrosis, the polymorphism of the cells and the cell degeneration. Though there are some resemblances between the cell type seen here and that of other reported cases, on the whole they are not marked, consisting in large part of the polymorphism of cell and the abundant fat vacuoles in the cytoplasm. In view of the rapid proliferation and degeneration present even in the better preserved portions, it is presumptive to interpret these as characteristics of the cell rather than of the proliferative and degenerative process. The illustration in the text resembles more a rapidly growing and degenerating embryonal tumor than one of interstitial cell origin and differs from the accompanying illustration of the proliferating interstitial cell foci in the other testicle. Also, the marked cell degeneration, the hemorrhage and necroses seen here have not been observed in the other cases reported.

VILLATA'S CASE (1928).—A testicular tumor was found arising in the descended right testicle of an underdeveloped man of 22. It was more than twice the size of a normal testicle. The opposite testicle was in the inguinal canal. Potency was retained. The patient had, in addition, hypospadias and bilateral inguinal hernia. The specimen consisted of a central necrotic portion and a peripheral ring of tumor tissue. The residual tubules were sparse and widely separated, showing absence of spermatogenesis and alterations of progressive atrophy. There were two types of tumor tissue present. Some areas were composed of large round cells with complete boundaries and a clear cell body containing large round or oval nuclei rich in chromatin. Between portions of this character were other areas of cells disposed in cords of varying size, occupying large uninterrupted areas. Tumor tissue of this second type prevailed. These portions were composed of polyhedral, ovoid or bizarre cells. The cytoplasm stained vivid rose with hematoxylin and eosin and was finely vacuolar. The vacuoles proved to be lipoid droplets. No lipochrome was found. The nuclei were small, irregular and less intensely colored than those of the large round cells.

Obviously this tumor was of a teratoid nature, the only interest in which is to show that neoplasia of the interstitial cells may occur as a derivative of teratoma testis.

SLANINA'S CASE (1930).—A tumor the size of a hen's egg developed over a period of eight years in a man who was 45 at the time the tumor was removed. It was 10 cm. in length, was hard and weighed 94 Gm. On section, it was bluish except near the periphery, where it was golden tan. The cells were round, and the protoplasm had numerous vacuoles. Many capillaries of one layer of endothelium were present. No seminiferous tubules were seen.

Though Slanina considered this a tumor of the interstitial cells, the briefness of his report renders impossible any definite statement as to its nature and origin. It seems, however, from the little given that the constituent cell bears not too close a resemblance to interstitial cells. The illustration in the text also is less suggestive of interstitial cell tumor than of seminoma.

The final recorded case is that of Panà, who in 1931 described a specimen obtained from autopsy material. Only little clinical data were available.

PANÀ'S CASE.—An ovoid, white, firm tumor, measuring 6.2 by 3.1 by 2.9 cm. and weighing 28 Gm., was found in the fully descended testicle of a 16 year old boy, who died of sepsis following acute otitis. The opposite testicle was undescended. Grossly, the tumor was seen to be divided into a peripheral, hard, whitish-gray cortical zone and a central zone of ocher with darker spots. The central zone projected irregularly into the cortical zone. Microscopically, the cortical zone was seen to be composed of the tunica albuginea, no longer individualized but augmented by large bundles of connective tissue fibers. Toward the internal aspect these were less compact. The central zone was made up of interlacing cell strings, having no regular arrangement. The cells were usually oblong or oval; some were polyhedral, and others, irregular or cubical. They were clear and vitreous and contained vacuoles that did not stain with the ordinary stains. The nuclei were round, rich in chromatin and medium sized. The cytoplasm in some cells contained brown-yellow pigment granules and more rarely, spherical acidophilic granules. In this central region the tissue was poor in connective elements, the stroma consisting only of reticulated pericellular fibers. In the zone of transition from the central to the cortical region, the stroma was abundant. In this intermediate part, small atrophic residues of seminiferous tubules were seen. No normal parenchymatous areas and no areas of distinct necrosis or containing diffuse hemorrhage were observed.

One has here a lesion of quite characteristic cellular components, although de Bary questioned that it was a neoplasm rather than merely advanced hyperplasia. However, he offered as evidence only the statement that tumefaction is unknown in a descended testicle when the other is undescended. That this is not so has already been seen, even in a case reviewed here (Villata's case). The architecture seen is that of a neoplasm, the tumor proper (central zone) being devoid of parenchymal elements which exist only in the subalbugineal region (transitional zone), as in a lesion expanding outward from a central focus. This differs from the picture encountered in the ordinary hyperplasias, and, as a matter of fact, from that present in the opposite testicle, which was reduced in size, weighing 3.5 Gm. The parenchyma was greatly reduced; the few residual tubules were small in volume, with the lumen either obliterated or narrowed to a small slit. Seminiferous cells were scarce. The connective stroma was proliferous, consisting of broad bundles crossing the whole organ radially. In the stroma the interstitial cells were abundant, forming small nodules in some areas.

THE INTERSTITIAL CELLS IN ANIMALS

Both hyperplasia and neoplasia of the interstitial cells have been reported in animals. Normally the degree of development of interstitial cells varies with the species and the nutritional state of the animal. In the boar, cat and mole they are numerous; in the elephant, less so. In the marmot they are absent during the period of winter sleep, but with resumption of activity they become almost as numerous as in the boar (Hansemann).

Hyperplasia of interstitial cells in cryptorchid horses has been reported by Pallaske and in cryptorchid rabbits by Bouin and Ancel. Experimentally, hyperplasia of the interstitial cells has been produced by Bouin and Ancel in rabbits by ligation of the vas with or without contralateral castration and in rats by chronic intoxication with alcohol or tuberculous toxin. In hybrid birds (hybrid of peacock rooster and guinea-hen) immense proliferation of the interstitial cells with relegation of the semen-forming elements to the background was reported by Poll.

Kunze reported the occurrence of lesions which he described as interstitial cell tumors in twenty-three dogs. These occurred in the atrophied testes of old dogs, were often multiple and bilateral and consisted of small nodules within and usually just beneath the albuginea of the testis, which was never enlarged. The nodules were yellow-white in contrast to the darker parenchyma. The larger ones showed hemorrhagic degeneration. They were enveloped by a capsule of connective tissue and were penetrated by a well formed capillary network. Connective tissue was scarce. The average nodule was the size of a pea; larger ones up to the size of a cherry were formed by a conglomeration of the smaller nodules. Atrophied seminiferous tubules were compressed between the growths. The nodules were composed of cells closely resembling interstitial cells. They were polymorphous, with granular cytoplasm filled with vacuoles. The lipoid stained with scarlet red, at times in quantities filling the entire cell. In four animals pigment was present. The nuclei were round or oval with one nucleolus.

These lesions were interpreted by the author as interstitial cell tumors. However, their multiplicity, bilaterality and small size, in addition to what has already been seen of hyperplasia in man, leave one reluctant to accept them as anything but node-forming hyperplasia. This view is fortified by Pallaske, who observed identical changes with a high degree of regularity in the atrophic testes of senile dogs. As long as spermatogenesis persisted, only a few interstitial cells were seen. With cessation of spermatogenesis and atrophy of the tubules, these lesions made their appearance. He described the pathogenesis of these nodules from strands of several layers of interstitial cells surrounding an atrophic tubule or tubules, which atrophied further and finally disappeared with further growth of the cells, leaving a new nodule. More-

over, he added, in dogs approaching senility, nodelike hyperplasias of the interstitial substance are a common finding in many organs (liver, spleen, pancreas, thyroid and adrenal gland). Using only healthy dogs, Pallaske performed complete autopsies and examined all the organs for analogous nodelike hyperplasia of the interstitial tissue. He found nodular hyperplasia of the interstitial cells in the testicles of thirty-one of one hundred and seven dogs and nodelike hyperplasia of the interstitial substance in other organs in seventy-one of the dogs. In twenty-eight of the thirty-one dogs with testicular nodelike hyperplasia, hyperplasia of interstitial substance was present in the other organs as well. He concluded that the testicular lesions observed by Kunze and himself were not real tumors but were rather analogous to the hyperplasia of interstitial cells observed in the testes of cachectic men. As a contrast, he then offered a case of actual interstitial cell tumor arising in the testes of a horse.

PALLASKE'S CASE.—Both testes were much enlarged and moderately firm. The left was 31 by 17 cm. and weighed 8 Kg. The right weighed 2 Kg. The structure of each testis was the same. The parenchyma was replaced by tumor tissue except in an occasional small area, which grossly was gray. These areas contained atrophic tubules with hyaline basement membrane embedded in broad bands of tumor tissue. The tumor tissue itself was composed of polygonal cells, rich in protoplasm and with chromatin-poor nuclei, often eccentrically placed. Mitosis were observed. The protoplasm stained well with eosin. In most cells the protoplasm contained finely granular yellow-brown pigment, which remained yellow-brown when the cells were stained with scarlet red. No clinical history was available except that there were no grossly obvious metastases. It was not known whether there was local involvement of the lymph nodes. Structurally, the tumor seemed malignant, though it had not invaded the tunica.

The author was of the opinion that the picture resembled a polymorphous sarcoma derived from the interstitial cells. Little comment is necessary except that the malignancy of the lesion is not established.

Interstitial cell tumor of the testicle was reported by Ball in two dogs.

The first tumor was found in an adult dog. The testicle was four times normal size. On section, the tumor was homogeneous and was surrounded by a fine fibrous shell, which pushed back the seminiferous tubules, the majority of which were in a state of involution. The neoplastic elements were grouped in perivascular collars, which attained considerable size. Elsewhere the vascular axes were rare, the tumor cells being arranged in extensive cellular sheets. The cells were irregularly oval or polyhedral. The nuclei were small, ovoid or spherical, with a delicate reticulum. The perinuclear zone was usually homogeneous or finely granular. Multiplication was slow, by amitoses, and was often incomplete. Occasionally plurinucleated cells were seen. Degeneration was observed in the regions of the diffuse cellular sheets. There the cells were smaller, and cytolysis, karyolysis and pyknosis were found. Granular masses of disintegrated cells were seen. The cytoplasm of the cells showed a more or less generalized alveolar architecture, and this Ball offered as evidence of their origin from interstitial cells. In some areas the cellular elements were more voluminous,

the appearance suggesting fat cells at times and cells of a glandular acinus at others.

The second tumor occurred in the testicle of an old dog. The tumor was as large as that in the first dog, and the histologic structure was identical, though not as clear because of the presence of numerous hemorrhages.

Peyron, in discussing these tumors, stated that they indubitably arose from the interstitial cells of the testicle. He offered no specific differentiating features, though he did stress the difficulty in distinguishing interstitial cell tumor from seminomas in diffuse sheets. Despite the assurance of Ball and Peyron as to the validity of origin of these lesions from the testicular interstitial cells, the histologic description offered is too cursory to warrant any definite conclusion. The illustration in the text, however, is very suggestive of interstitial cell neoplasm.

REPORT OF AUTHOR'S CASE OF INTERSTITIAL CELL TUMOR OF THE TESTICLE

A 35 year old man was admitted to the hospital with the complaint of a protuberance in the right groin of two months' duration and one in the left groin, which appeared shortly thereafter. Cough and work made these protrusions more prominent. Exertion caused pain in the right groin. The patient also stated that his left testicle was considerably enlarged, having been so for fifteen or twenty years. The right testicle was somewhat small and had not grown at all in size in this period.

Potency was intact, but though the patient had been married for ten years there had been no children. Examination of a condom specimen eight years before his admission was said to have revealed live spermatozoa.

The patient had come to the United States from Poland twenty years previously. His habits were regular. The medical history was irrelevant. He had injured his nose and lacerated his upper lip twenty years before in a fall from the roof of a porch, but he said that he had not injured his testicles at that time. Eleven years later a nasal operation had been necessary to relieve obstruction. The systemic history was unimportant. The patient said that he had never had venereal disease or any symptom of it. The family history was noncontributory.

Physical examination revealed a well nourished white man of 35, who did not appear ill. The habitus was masculine, and the secondary sex characteristics were normal. The head was normal, except for the presence of pyorrhea and dental caries. No nodes, masses or abnormal pulsations were present in the neck. The heart and lungs were normal. Abdominal examination revealed only small indirect inguinal hernia bilaterally. The skin, extremities and osseous, lymphatic, arterial and neurologic systems were normal. Rectal digital examination revealed only a moderately enlarged prostate, especially the left lobe. The right testicle was small and insensitive. The left was twice normal size and was firm and solid. Its epididymis was slightly enlarged. Both testes were fully descended.

Urinalysis gave negative results. The blood pressure was 118 systolic and 78 diastolic. Hormonal studies were not made.

A modified Andrew's hernioplasty was performed bilaterally, and orchidectomy was done on the left side. The postoperative course was entirely uneventful. Both wounds healed by primary union, and the patient was discharged on the fourteenth postoperative day. The pathologic diagnosis, made by Drs. Klemperer and Otani, was interstitial cell tumor of the testicle. Because of the possibility

of malignancy, even though not warranted by the clinical course and histologic picture, a course of radiotherapy was administered to the pelvis, the mediastinum and the spine for three months after the patient's discharge.

The results of the pathologic examination follow: The testicular mass, stripped of its appendages, measured 6.5 by 6 by 3.5 cm. after fixation. The albuginea was intact, somewhat thickened and pinkish white. The mass was solid and firm. On section (fig. 1) it was seen to be composed almost entirely of tumor, with the exception of a small gray-brown, nonpigmented area at the lower pole, which was completely demarcated from the tumor proper by a thin fibrous capsule which fused with the albuginea. This area ostensibly consisted of compressed, atrophic, residual testicular tissue. The tumor had a glistening, cellular appearance. It was dark brown with a greenish cast, with here and there small gray areas. It was irregularly divided by fibrous septums derived from the albuginea. The epididymis and vas deferens were not remarkable.

Fig. 1.—Gross view of a cut section of the tumor (long axis oblique). Note the testicular rest—the light area in the lower left hand corner.

Microscopically, the tumor tissue was seen to be composed of anastomosing strands, nests or broad sheets of epithelioid cells. Often the arrangement was alveolar, resembling salivary gland; in other places the resemblance to liver was striking (fig. 2 *A*). The stroma was sparse, consisting of a fine reticular tissue surrounding the pseudo-alveoli and the anastomosing cell cords. Numerous capillaries of one layer of endothelium were present in intimate relation to the cell cords. They were often turgid with blood, and occasionally small extravasations were observed. No necroses were seen.

The individual cells (fig. 2 *B*) were large, though quite variable in size. They averaged about eight to fifteen times the size of a red blood cell, though many were larger. Their state of preservation was good, little or no degeneration being seen. The cells were polymorphous and polyhedral, ovoid, round or irregular. The nuclei were also variable in size and small in proportion to the abundant cytoplasm. Most frequently they were about one to three times the size of a red cell, though many were larger, and occasional giant forms were seen. Rarely, two nuclei were seen in a given cell. They were usually oval or round. The chromatin was sparse, though also variable in intensity. Usually one or none, though occasionally two, nucleoli were present. The nuclear membrane was well

defined. No mitoses were seen. The cytoplasm was abundant, acidophilic and finely granular. Most cells contained brown or brown-yellow, fine to coarse pigment granules. The pigmentation was of varying intensity, often obscuring the cytoplasm completely, while in other cases it was evidenced only by a fine brownish stippling. The pigment was a lipochrome, as indicated by negative reactions to iron and melanin and an intensification of staining to a golden brown with sudan IV. Some cells contained in addition to the pigment a small amount of neutral fat in the form of small droplets. No Reincke's crystalloids were seen.

There was no invasion of the albuginea or of the gray-brown nodule, which proved to be compressed parenchymal residue. It consisted of a collection of

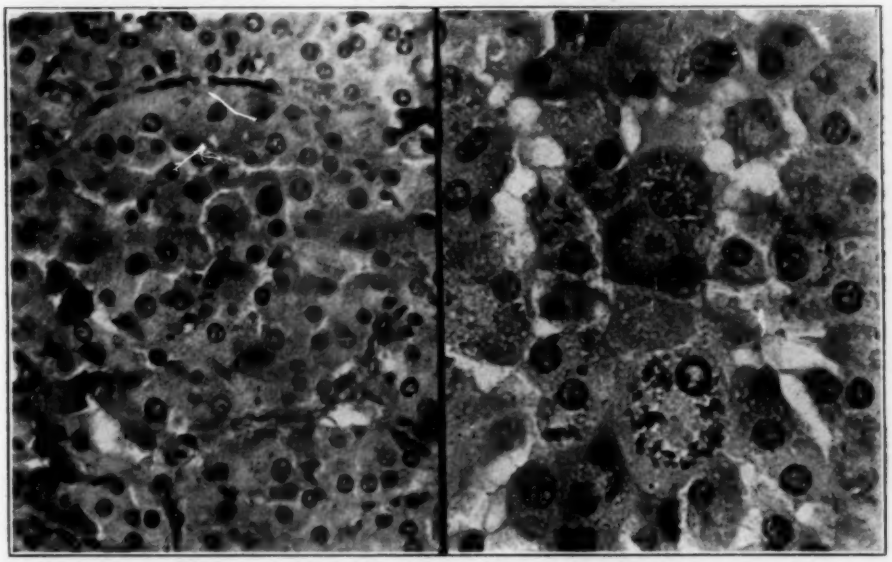

Fig. 2.—*A*, low power photomicrograph of a section of the tumor; hematoxylin and eosin. Note the "liver-like" arrangement, the variability in the size and shape of the cells, the variability in size, shape and staining intensity of the nuclei, the abundant cytoplasm and the capillary encircling a group of cells in intimate relation to them. *B*, high power photomicrograph; hematoxylin and eosin. Note the pigment in the cells.

atrophic, compressed seminiferous tubules, with slightly thickened membrana propria of an intact outer elastic layer and an inner, slightly augmented, collagenous layer. The epithelium was atrophic, showing only one to two layers of seminal cells. The seminal lineage was always incomplete, and no sign of spermatogenesis was seen. Sertoli cells were present. No interstitial cells were present between the tubules. The intertubular stroma consisted of a small amount of fibrous tissue, which centrally was compressed into a thin fibrous layer, forming the capsule which separated the testicular rest from the tumor proper.

How completely the cell type observed in this case resembles the interstitial cell is apparent. Both the clinical history and the histologic picture speak for a benign lesion.

COMMENT

It is seen how rare an entity tumors arising from the interstitial cells of the testicle are. Since the existence of tumors of this nature was first suggested by Waldeyer in 1872, only a relatively few reports of tumors of this type have found their way into the literature. In only six of the cases reported can the growth be considered as indubitably arising from the interstitial cells—the case of Chevassu, the two cases of Kaufmann, the case of Masson and Sencert, the case of Panà and the case here presented. The tumor in Dürck's fourth case and in de Jong's case may possibly also belong to this group.

In the last analysis, the etiology of these growths is of course unknown. No feature of apparent etiologic significance was present in the cases of Masson and Sencert and of Panà and in the case reported here. However, certain features were present in the other cases which may possibly have some causal bearing. Kaufmann's patients were brothers. In one, the lesions were bilateral, and in the other, possibly so. A hereditary congenital basis is suggested here. In Chevassu's case the growth occurred in an inguinal testicle in sequence to a previous operation for hernia on that side. Testicular tumors are about one hundred to one hundred and fifty times as frequent in undescended as in descended testes, and the trauma of the operative procedure may have been an additional factor. On the other hand, parenchymal atrophy with secondary hyperplasia of the interstitial cells of varying degree occurs commonly as an accompaniment of ectopic testicular position, and one must therefore keep in mind the possibility that tumor formation may occur on the basis of a previously existing hyperplasia.

Although individual cases may differ in details, the microscopic picture is really sufficiently characteristic to permit the isolation of a special independent form of tumor. In general, there seems to be no preferred age group, the cases reported occurring in persons from 16 to 62 years of age. One growth occurred in an undescended testicle; the other five, in fully descended testicles. The color, depending on the presence or absence of pigment and the amount of fat, was variable. It was reddish yellow in Chevassu's case, grayish in Masson's, brownish red in Kaufmann's, ocher in Panà's and dark brown with a greenish cast in the case reported here. In all instances the gland was enlarged.

Microscopically, the testicular parenchyma was absent entirely or had been reduced to a few atrophic subalbugineal tubules, enveloped in an imperfect fibrous shell which segregated them from the tumor proper and fused peripherally with the albuginea. In my case the residual testicular tissue was limited to a small rest at the lower pole of the mass, which was separated from the tumor by a fibrous capsule

which anastomosed with the albuginea. Where no parenchyma remained, the tumor was limited by the albuginea, which it was never observed to have invaded. Proliferation of interstitial cells such as is ordinarily present in cases of diffuse hyperplasia was always absent between the residual tubules.

The tumor masses were broken into lobules by fibrous septums projecting from the albuginea. The tumor tissue consisted of broad anastomosing cords or large sheets of cells of somewhat epithelioid appearance. The cell type and arrangement were often very suggestive of liver, adrenal cortex or an alveolar tumor of the carotid or salivary gland. The stroma was sparse, consisting of reticular tissue and thin-walled capillaries, often in intimate relation to the tumor tissue. Necrosis and hemorrhage were rare.

The constituent cells were large, though they varied in size. They were polymorphous; usually polyhedral forms were present, though round, cubical and irregular forms were common. The cytoplasm was abundant and homogeneous or granular and contained various inclusions. Fat droplets were usually present in varying amount, at times giving a foamy appearance to the cells. Pigment was not constant. Highly refractile granules having the appearance of secretory granules were present in some tumors. Reincke's crystalloids were never observed. This last was expected, since, according to Lubarsch, these bodies are not present in diffuse testicular processes such as tumors.

The nuclei were relatively small and varied in size. Both relatively and absolutely they were smaller than those found in seminomas. They were vesicular, with a sparse chromatin network of varying intensity, and contained one or two nucleoli. Cell division, both amitotic and mitotic, and occasional plurinucleated cells were observed.

The essential features isolating hyperplasia of the interstitial cells of the testicle from other testicular growths are the polymorphism of the cells, their large size, their abundant cytoplasm, containing lipoid and inclusions of various types, the small chromatin-poor nuclei and the liver-like arrangement. These are sufficient to enable differentiation from other testicular tumors with which these growths may be confused, particularly seminomas and heterotopic adrenal tumors. Hyperplasia may be distinguished by the presence of an etiologic factor, by the diminished testicular volume and by the focal intertubular situation of the proliferating cells.

The treatment, as with other testicular tumors, is orchidectomy. This should be followed by postoperative irradiation because of the possibility of malignancy, despite the fact that in only one case (Masson's) was the growth clinically malignant.

SUMMARY

The interstitial cells of the testicle may be the source of hyperplastic or neoplastic lesions. The characteristic cell is of variable size, is polymorphous and contains abundant cytoplasm, with various inclusions, and a relatively small nucleus poor in chromatin.

Hyperplasia occurs secondarily to atrophy of the testicular parenchyma due to some general or local condition. The proliferation is always focal though diffuse, and intertubular, though parenchymal atrophy may have progressed to such a degree as to make the intertubular situation of the proliferation not readily appreciable. The testicle is usually considerably reduced in size.

Neoplasia of the cells of Leydig is an extremely rare condition and is frequently confused with hyperplasia and with seminoma. The characteristic features of this type of growth are the cell type, the enlargement of the testicle, the absence of an etiologic factor for primary parenchymal atrophy and secondary hyperplasia of the interstitial cells, the demarcation of the lesion from the residual testicular tissue, if present, and the absence of proliferation of interstitial cells between the residual tubules. Though usually benign, the growth may be malignant.

Hyperplasia and neoplasia of the interstitial cells of the testicle in animals are briefly reviewed.

A case of interstitial cell tumor of the testicle in a 35 year old man is reported.

ADDENDUM

Since this article was submitted for publication, there have appeared two further references to interstitial cell tumor of the testicle, and one additional case, previously published, has been called to my attention. For completeness, brief comment on these will be made.

Rowlands and Nicholson reported a case of tumor of the left testicle and macrogenitosomia in a 9 year old boy. The involved testicle measured 5 by 4 by 3.5 cm. No testicular tissue was apparent grossly. The tumor was firm, faintly granular, homogeneous and brownish, with small hemorrhages. The only testicular tissue present was some atrophic subalbugineal tubules separated from the tumor tissue by a fibrous capsule. The tumor was composed of irregular bands and nodules of large closely packed cells separated by strands and sheets of noncellular hyaline stroma. The cells varied in size and shape. The cytoplasm was homogeneous and intensely acidophilic, with degeneration (hydropic and vacuolar forms) common. The nuclei were relatively small and deeply stained, with a fine chromatin network and one or more nucleoli. Many cells were binucleated or multinucleated. Fine granular brownish pigment was present in many cells, and stains for fat showed needle-shaped crystals and small rods in the cytoplasm.

The patient was seen two years after orchidectomy, at which time there was no evidence of recurrence or metastasis. No regression in the signs of puberty had occurred.

Rowlands styled this tumor an adenoma of the interstitial cells of the testicle and attributed on the basis of it an association between the interstitial cells and the development of secondary sex characteristics. The cell type cannot be disputed, but in view of the failure of the premature genital and bodily growth to regress and in view of the absence of studies to eliminate the possibility of some lesion elsewhere that might cause the premature development, one cannot conclusively attribute the precociousness to the growth removed.

Stewart, Bell and Roehlke reported a case of testicular tumor and hypergenitalism in a 5 year old boy. This tumor was a nodule, measuring 1.8 by 1 cm., demarcated from the adjacent testicle, which was somewhat enlarged. The other testicle was normal in size. The tumor consisted of cords and sheets of large cells, with spongy cytoplasm and compact nuclei. The testicular parenchyma showed premature development of the seminiferous tubules. There were no cytoplasmic inclusions. On removal of this testicle there occurred some regression in the size of the penis and disappearance of the pubic hair. Clinically, a roentgenogram of the sella turcica showed a normal picture, no calcium was seen in the region of the pineal body and an intravenous pyelogram revealed nothing significant. The authors concluded that the tumor was derived from the interstitial cells and that the excessive genital development was produced by the excessive secretion of the cells composing the tumor.

The cell type found in this tumor is not completely characteristic, lacking the polymorphism of cells and the cytoplasmic inclusions. The illustration in the text, though, shows cells resembling most the interstitial cell. The conclusions, however, as to the relationship of this tumor to the premature development are not warranted. First, the clinical studies do not quite rule out another focus. Second, the premature development of the testicular parenchyma may well have been the causal lesion rather than one arising secondary to the tumor nodule found. Recent studies have resulted in evidence rather against the interstitial cells as a source for androgen, its production being attributed instead to either the Sertoli cells or the germinal epithelium itself.

Budd reported a case of gynecomastia and impotence accompanying a testicular tumor 25 cm. in diameter in a 42 year old man. He said that the tumor microscopically was composed of interstitial cells, but no description of the cells was given. Bell, in discussing the case, stated that the structure of the cells was that of an embryoma of the testis rather than that of an interstitial cell tumor.

One additional case is referred to by Stewart, Bell and Roehlke in their article. This is a case reported by E. Sacchi. A 9 year old boy had the somatic and genital development of an 18 year old youth. There was a tumor of the left testicle measuring 55 cm. in circumference. The tumor is poorly described. According to Sacchi it consisted of masses of cells of an epithelial appearance and alveolar arrangement. The cells had large nuclei and abundant granular cytoplasm. Corpuscles of various sizes were present in the cytoplasm, nuclei and stroma. These, the author thought, were coccidia. He labeled the growth an epithelial tumor with coccidiosis. Orchidectomy was followed by a regression of the beard, the hair on the arms and legs, the deep voice and the erotic tendency that had previously been manifest.

Stewart and his co-workers, in discussion, stated that the pathologic interpretation was incorrect and that the tumor was really an interstitial cell tumor. They arrived at this conclusion largely on the basis of the bodily changes which occurred on removal of the tumor. This, however, seems to be reasoning after a fact which in itself is not established. F. Parkes Weber referred to the same tumor as a carcinoma-like tumor. He further stated that it would be interesting to know whether any testicular tumors in such cases (macrogenitosomia) could justifiably be regarded as endocrine primary tumors of the interstitial cells.

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17 East Ninety-Sixth Street.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

FRANK HINMAN, M.D.
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.
BUDAPEST, HUNGARY

ALEXANDER B. HEPLER, M.D.
SEATTLE

ROBERT GUTIERREZ, M.D.
NEW YORK

GERSHOM J. THOMPSON, M.D.
AND
JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

(Concluded from page 832)

BLADDER

Carcinoma.—Bumpus and Silver [38] reviewed all cases of tumor of the bladder observed at the Los Angeles County General Hospital between June 1927 and June 1934. The last date was chosen in order that at least two years might elapse after the last treatment and the final results could be accurately evaluated. There were 135 cases in the group. In 36 the carcinoma was so far advanced that no surgical treatment could be employed, and in 8 merely palliative cystotomy was undertaken; all of the patients died in the hospital. The group of 99 remaining cases seems sufficiently large to suggest what is accomplished by the present methods of treatment in large charity hospitals with constantly changing visiting staffs. Eighty-nine per cent of the patients were traced for from three to five years.

Destruction with diathermy was used in 77 of the 99 cases, in 34 through the urethra and in 43 by transvesical exposure. In the former group of cases 17 of the patients were living from three to five years after transurethral electrocoagulation (50 per cent of apparent cures); 11 were known to be dead, and the condition of 5 could not be checked;

38. Bumpus, H. C., Jr., and Silver, Barney: Tumors of the Bladder, J. Urol. **37**:141-147 (Jan.) 1937.

moreover, 2 of the 11 who were known to be dead lived more than five years before they succumbed to recurrences.

The tumors in 25 of the 43 cases in which transvesical treatment was used were of the papillary type; in this group 16 of the patients were known to be dead and 7 had lived more than three years. In 18 of the cases the tumors were of the infiltrating type; in this group 14 of the patients were known to be dead and but 1 was known to be alive more than three years after operation. Fourteen patients (35 per cent) died as a result of the operative procedure. Since at least 8 patients were alive from three to five years after the operation and 30 were known to be dead, there would seem to be approximately a 19 per cent possibility of cure by this method. Improvement of results in the future must evidently come from a reduction in the operative mortality, so that 35 per cent of the patients are not immediately eliminated from all possibility of cure. Some surgeons have felt that the high mortality was largely due to involvement of the ureteral orifices in the destruction produced by the cautery. In 13 of the 34 cases in which the patients were treated transvesically, it was noted that the ureteral orifice had been included in the destruction, but the convalescence was affected in only 1 of the cases. In the series in which transvesical treatment was employed a ureteral orifice was included in the destruction produced by the cautery in 29 cases, and in 10 cases it was considered a decided factor in an unsatisfactory convalescence if not a direct cause of the patient's death. In the series of 29 cases in which the lesion was inoperable, the extensive destruction produced by cauterization involved the ureteral orifice in all the cases in which death occurred, and in several cases the resulting inflammatory process extended along the course of the ureters to the perivesical tissue. Certainly, wherever possible, the insertion of a catheter into an involved ureter and its retention there during the first days of convalescence should be an aid in reducing the high mortality of transvesical thermal destruction. Apparently such destruction is best accomplished by diathermy, for of 8 patients treated with the Percy cautery 4 died immediately after operation, and 2 others were known to have died later.

Kraas [39] described in detail a case of cystadenoma of the bladder. Differential diagnosis of this condition and endometriosis was difficult and could be made only by the pathologist. Endoscopic resection with coagulation of the base of the tumor was successful and effected complete recovery. The symptoms were those of a tumor of the bladder with exacerbation during the menstrual periods.

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39. Kraas, Ernst: Cystadenom der Blase-endovesicale Exstirpation, Ztschr. f. urol. Chir. u. Gynäk. **42**:411-415 (Dec.) 1936.

Chauvin [40] reported a case of tumor of the bladder with an adenomatous structure in a man aged 51. The tumor, which was composed mostly of connective tissue fibers, contained irregularly disseminated glandular acini, lined with a double layer of cuboid and often cylindroid cells; most of the acini were empty, and a few were filled with a homogeneous exudate which had the staining reactions of mucin.

Only 23 cases of vesical adenoma have been reported in the literature. The glandular structure of such tumors is so varied that one may say there is no uniformity of type. It is impossible to deny that they are glandular, notwithstanding Sappey's assertion that the normal mucosa of the bladder contains no glands. Various other authors, however, have examined glands in the wall of the bladder microscopically, and although the histologic structure has been variable, the topography was nearly the same; the glands were strictly localized in the vicinity of the neck of the bladder, from which they may invade the trigon and the anterior aspect of the bladder. Cruveilhier alone maintained that they could be found in any part of the wall of the bladder, and Chauvin's present case, in which the tumor was behind the ureteral orifice, seems to substantiate this claim.

In structure, these tumors may be simple evaginations of the mucosa; they may be of prostatic type, as if representing aberrant lobes of the prostate; some have been found composed of true mucous glands, better differentiated, but always of small size and of acinous or tubular structure; others have been lined with epithelium of intestinal type. It must be admitted that these glands are not found in all persons; they are rare, and the tumors to which they give rise are exceptional. They have been attributed by some authors to irritation or local inflammation. Some of the tumors resemble adenoma of the prostate, some are of tubular appearance and some are cystic adenomas. In short, the tumors are anomalies, and it would be difficult to try to establish any general rule with reference to their formation.

Kutzmann [41] stated that leiomyoma of the bladder, as well as other mesothelial tumors of the bladder, is rare. The leiomyoma is a benign growth of the smooth muscle; its etiology and pathogenesis have been but vaguely explained on the basis of embryonic rests. The usual symptoms may be hematuria, disturbances in micturition and an associated feeling of pressure in the bladder. In some cases there have been individual leading signs or symptoms, as in the case observed by the author in which the tumor protruded through the urethra and caused subsequent subcapsular hemorrhage. Diagnosis can be made by routine urologic procedures. The condition in the female is not to be confused

40. Chauvin, E.: Tumeurs vésicales a structure d'adénome, J. d'urol. **42**:521-531 (Dec.) 1936.

41. Kutzmann, A. A.: Leiomyoma of the Urinary Bladder, J. Urol. **37**:117-132 (Jan.) 1937.

with pelvic disease, and that in the male is not to be confused with benign hypertrophy of the prostate gland. Treatment consists of endovesical procedures or cystotomy with wide resection of the involved wall of the bladder. Prognosis is good, since nearly all leiomyomas of the bladder remain benign. A proved instance of leiomyoma of the bladder is reported.

Colston and Leadbetter [42] reported a case of metastasis of carcinoma of the bladder to the brain. The interesting feature in this case was the remarkable response of the extremely malignant primary growth to high voltage roentgen therapy and to radium therapy; although no gross evidence of tumor was present at a careful necropsy, microscopic sections revealed that viable cancer tissue was still present in the deeper portions of the wall of the bladder. Evidence of metastasis to the brain became apparent soon after treatment was completed and rapidly determined the fatal outcome. Studies of the literature have shown the rarity of reports of cerebral metastasis in cases of tumor of the bladder. The similarity of this case to that reported by McKay is striking, in that in both instances there was a remarkable response shown by the original tumor to high voltage roentgen therapy and radium therapy, although in neither instance was the local growth entirely eliminated. Furthermore, metastasis to the brain occurred in both cases and was responsible for the fatal outcome. There was no evidence of metastatic deposits elsewhere in the body.

Rathbun [43] reported 91 cases of carcinoma of the bladder, in 63 of which the condition was proved and complete histologic data were presented. The histologic classification was epidermoid carcinoma in 45 per cent, papillary carcinoma in 29 per cent, adenocarcinoma in 16 per cent and scirrhous, medullary and undetermined types in 10 per cent of the cases. The author's results have been far from encouraging. Fifteen patients were alive and, with one exception, free from any signs or symptoms of recurrence at the end of three years. However, in the next two years 8 of these patients had recurrences and died, which left a five year salvage of only 7 patients (11 per cent).

As to the diversity of published results, these vary from results no better than Rathbun's to as high as 45 per cent of control. Some of the reports are based on a three year cure. This, Rathbun stated, is wrong. He was sure there is a heavy mortality between the three and the five year period. He also stated that considerable confusion exists as to what constitutes carcinoma of the bladder and how the tumor should be graded in relation to the degree of malignancy.

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42. Colston, J. A. C., and Leadbetter, W. F.: Brain Metastasis in Carcinoma of the Bladder, Tr. Am. A. Genito-Urin. Surgeons **29**:261-272 (May) 1936.

43. Rathbun, N. P.: Comments on Bladder Carcinoma: Classification—Prognosis—Treatment, Tr. Am. A. Genito-Urin. Surgeons **29**:255-260 (May) 1936.

He expressed the opinion that when practicable all cancers of the bladder should be radically excised. This would appear a simple position to take if it were not for the fact that because of their usual situation only a small percentage of such carcinomas lend themselves to this type of treatment. The fact that the growth invades one ureteral orifice should be graded in relation to the degree of malignancy.

In the present wave of enthusiasm over transurethral operation there is a decided trend toward the employment of the cystoscopic approach in these cases. This may easily be overdone. This approach should be reserved for very small growths, particularly small recurrent growths. The application of more than four radium seeds through the cystoscope has been rather unsatisfactory. For one reason and another, especially bleeding, it is difficult or impossible to implant them with any degree of accuracy.

As carcinoma remains confined to the bladder, with no disposition to extend by metastasis or otherwise for a considerable period of time, total cystectomy would seem the ideal treatment. The operation per se is not technically difficult, but there are two rather formidable obstacles to overcome. The first is the disposition of the ureters. Ureteral transplantation to the bowel, even in the most skillful hands, carries with it a mortality which is almost prohibitive, transplantation to the groin or bilateral nephrostomy leaves a state of affairs which is far from ideal. This leads one to the second obstacle, which is the selection of cases. The cases in which the condition is very advanced are hardly ideal, in spite of the fact that most total cystectomies are done in this group. Some of the cases in which the condition is not so far advanced might seem to be eminently suited for this operation if it were not for one important item: There is no question but that in some of these cases the condition is entirely and completely controlled by radium, and one certainly hesitates to condemn any human being to total cystectomy with all of its implications if there is even a remote chance of saving the bladder.

Roentgen therapy is still in its infancy. Modern roentgen therapy is a powerful agent and has potentialities for evil as well as for good, as is evidenced by the fact that within the past year one of Rathbun's patients died directly from its effect and another presented alarming symptoms for several weeks. It remains for the future to determine its place in the therapeutic armamentarium.

Graves, Kickham and Nathanson [44] expressed the opinion that the bladder should be considered an integral part of the problem of carcinoma of the uterine cervix because of the great frequency with which

44. Graves, R. C.; Kickham, C. J. E., and Nathanson, I. T.: The Bladder Complications of Carcinoma of the Cervix, Surg., Gynec. & Obst. **63**:785-793 (Dec.) 1936.

it is involved by the disease itself or as a result of treatment. They recommended cystoscopic inspection in the routine examination in all cases before instituting therapy and at intervals thereafter. By this means, when the bladder is found to be normal a base line will be afforded for comparison with later observations as the carcinoma progresses. When, on the other hand, intravesical invasion is found to have taken place, the diagnosis as regards the extent of the disease at once will be rendered more accurate, and information of definite prognostic value also will be obtained. It should be emphasized, however, that extension of the disease into the bladder from the cervix should not be considered a deterrent to vigorous treatment of the malignant process. The authors reported 1 unusual case in which there was extension even to the point of vesicovaginal fistula at the time of the first examination. After treatment there was no evidence of active carcinoma. The fistula remained of course, but that is not too high a price to pay for successful cure.

Farrell and Fetter [45] studied 72 cases of carcinoma of the bladder; 67 of the patients were males and 5 were females. At the time of the report, 27 of the patients were still alive and under observation, 3 (4.1 per cent) for five years or more and 25 (34.7 per cent) for from one to five years; 45 were dead. In 70 cases the diagnosis was confirmed by histologic examination of tissue. Contrary to experience with carcinoma generally, in a case of carcinoma of the bladder the younger the patient, the better the prognosis. The disease is rapidly fatal, for of the 45 patients who died, 23 (51.06 per cent) were seen within three months of the onset of their first symptoms, and 13 (28.86 per cent) were examined with the cystoscope. The earlier the initial cystoscopy, the better the prognosis. In 32 (45.40 per cent) of the cases the tumor was inoperable and irradiation was the only available treatment. Irradiation relieves symptoms, particularly hematuria. Because of the rapidly fatal termination in most cases of carcinoma of the bladder, more radical operation and larger doses of radiation would appear to be justified.

Stone.—Siddall [46] studied the cases of vesical calculus in the records of the Canton Hospital from the standpoint of etiology.

In Canton, China, and the surrounding countryside, the one endocrine disease that is rather common is a disturbance of the thyroid gland, including simple goiter, hyperthyroidism and toxic goiter, hypothyroidism and adenoma. Thus, there exist in the same localities some cases of thyroid disease and an abundance of cases of urinary lithiasis. Hyper-

45. Farrell, J. T., Jr., and Fetter, T. R.: Roentgen Irradiation in Carcinoma of the Bladder: A Series of Seventy-Two Cases, J. Urol. **37**:133-140 (Jan.) 1937.

46. Siddall, A. C.: Primary Vesical Calculus, J. Urol. **37**:268-279 (Feb.) 1937.

parathyroidism with general decalcification has not been reported from the Canton Hospital. Nephrolithiasis has been associated with hyperparathyroidism. The stones in such cases, however, are renal; so it is not likely that the parathyroid glands are a factor in the production of stones in South China, where the stones are primary vesical calculi and are composed mostly of uric acid and urates.

There is a tendency today to attach a great deal of importance to vitamin deficiency as a cause of the formation of urinary calculus in man. In South China the findings do not indicate that the people who suffer from vesical calculus also suffer from either vitamin A deficiency or vitamin A and vitamin D deficiency. The Chinese farmer who has a vesical calculus usually takes an abundance of fresh vegetables. More significant, however, is the fact that most of the calculi seen in South China are composed of uric acid, urates and oxalates and form in acid medium, while the calculi formed in the bladder of the rat that is on a diet that is deficient in vitamins A or A and D are mainly composed of calcium phosphates and carbonates. The one disease due to vitamin deficiency that is common in Canton is beriberi.

The possible relation between a high calcium intake and urinary lithiasis has been pointed out previously. With this in mind, a survey was made of the source of the water supply in Canton and the surrounding country. In Canton, where vesical calculus is not so frequent, it was found that the river water, which is used by the poorer classes for cooking and making tea, is low in calcium. On the contrary, in the rural districts, where calculus is common, the household water supply is from wells, and this well water is extremely hard. The elixir of life for the southern Chinese is tea. The long-established habit of drinking tea and the fear of drinking raw water probably grew up from the observation that those who drank raw water were subject to frequent disastrous diseases. The ingestion of caffeine in the tea stimulates the excretion of endogenous uric acid, and a farmer who drinks 1,300 cc. of tea a day consumes from 2 to 4 grains (0.13 to 0.26 Gm.) of caffeine daily, provided all the caffeine is dissolved in the water.

Urinary calculi in inhabitants of South China are vesical and rarely renal. Apparently, the habits of eating, drinking and working in this section supply the fertile soil in which primary vesical stones are easily grown. The urine is concentrated, and uric acid and oxalates are present in relatively large amounts. It is possible that the factor which actually plants the seed or nucleus of the stone is recurrent albuminuria. It has been shown by Nicols and Hoecker that strenuous exercise at times can cause severe albuminuria in a normal subject. If this is true, it is certain that the Chinese farmer who works hard with his hands must have recurrent waves of albuminuria just at the time when the factors are operating to increase the excretion of endogenous uric

acid. When the Chinese farmer works the hardest he eats more vegetables, which increases the excretion of oxalate in the urine. It is further suggested that the albuminuria may disturb the protective colloids in the urine and cause precipitation of the uric acid and oxalate. But these constituents must stick together in order to form a nucleus, and time is required. In other words, a certain amount of stagnation of the urine is required, and the most likely place for such stagnation is in the bladder instead of in the kidneys. The farmer of southern China perspires freely, and it may be hours before he voids a small amount of urine. Perhaps many times soft balls of urates and oxalates held loosely together by the albumin are broken and voided, but sooner or later one bit will remain in the bladder an abnormally long time and form the nucleus of a stone.

Bilharziasis.—Giraud and Crosnier [47] reported a case of filariasis and bilharziasis in a Senegalese soldier. The latter infection was observed in three stages, of primary, secondary and tertiary lesions. The presence of filariasis was revealed by the characteristic chyluria without lipuria; the chyluria was of parasitic and not of tumorous origin. In view of the successive findings, it was believed that the chyluria was due solely to the filariasis and that the transitory presence of blood in the urine was due to the bilharzial parasite, while the presence of leukocytes in the urine was due to the combination of the two infections. The fair condition of the patient and the absence of anemia suggested that the bilharziasis had not been present long and that the parasite had been rather recently acquired.

The essential feature in the case was the demonstration of the chyluric syndrome, since the etiology of this condition has not always been so well proved. In the case under consideration Filaria Bancrofti was found not only in the blood, especially at night, but in the urine from the left kidney, while the urine from the right kidney was normal. Roentgenograms made after injection of an opaque substance into the left kidney revealed extracalical images which the authors did not hesitate to interpret as injected intraparenchymatous lymphatic canals. The pyelograms were sufficiently clear to give an idea of the site of the lesions in the left kidney. This unilaterality of the lesions has been pointed out by several authors. Giraud and Crosnier can thus confirm the opinion of those writers who say that chyluria does not always come from the bladder. They upheld the possibility of a mechanical theory for parasitic chyluria, without any necessary pathologic action of the microfilaria. The injected lymphatics were larger than normal; they were the site of true varices, due to obstruction of their lumens, which were caused by the parasites which had found their way into

47. Giraud, D., and Crosnier, R.: Bilharziose vésicale et filariose urinaire, J. d'urol. **42**:501-510 (Dec.) 1936.

the excretory passages of the kidney, where they produced chyluria. The authors also observed that the opaque substance itself appeared to have some curative action on the infected urinary tract, irrespective of whether a solution of sodium iodide, sodium bromide or silver nitrate was used. This idea was first put forward by the Japanese, Inoue, who attributed the efficacy of the treatment to the irritating effect of the substance injected. He advised continuing the instillation until a slight sensation of pain betrays its entrance into the lymphatic fistula. The authors, without knowing it, realized these conditions in making the pyelograms, and in their opinion this is the reason that the chyluria disappeared after a single instillation of a few cubic centimeters of the sodium salt of diiodomethane sulfonate.

The premature departure of the patient made it impossible to check the permanent results. It is well known that these infections are likely to recur. The mode of action of the injection is not known. The authors suggested that it may serve to obliterate the lymphatic fistula by a reactive edema. Its action seems comparable to that of sclerosing injections into varicose veins.

Cystitis.—Randall and Campbell [48] reported 5 cases of cystitis with alkaline incrustation in females in the absence of an obstructive lesion. The main method of relieving the symptoms of this type of cystitis and of obtaining a permanent cure is acidification of the entire urinary tract, regardless of the causative organism. The variability of the p_H of the urine from separate renal pelves was emphasized. The necessity for acidification of the upper part of the urinary tract, whether or not it is infected, is exemplified by the results of the treatment in the cases reported. Acidification of the urinary tract cannot be obtained by the oral administration of drugs or by acid-producing diets in the presence of cystitis with alkaline incrustation. Supplementary irrigations with acid solutions are necessary to foster an acid atmosphere, which may then be maintained by acid-producing drugs. In their experience, phosphoric acid has been the most satisfactory vesical irrigant to produce an acid medium. A 1 per cent solution is suggested for the bladder and a 2 per cent solution for the renal pelves. The pelves of the kidneys are most tolerant to this solution, but the bladder may at first rebel, in which case weaker acids are used to build up the tolerance of the bladder until solutions of phosphoric acid are accepted.

Dysfunction of the Nervous System.—Creevy [49] stated that a number of diseases of the nervous system may, by lessening the acuity of sensation in the bladder, lead to infrequent micturition, overdistention

48. Randall, Alexander, and Campbell, E. W.: Alkaline Incrusted Cystitis, J. Urol. **37**:284-299 (Feb.) 1937.

49. Creevy, C. D.: The Treatment of Neurogenic Vesical Dysfunction Complicated by Lesions of the Vesical Outlet, J. Urol. **37**:513-517 (April) 1937.

of the bladder, deficient oxygenation of the detrusor urinae muscle and loss of expulsive force. The development of an obstructive lesion at the vesical outlet will cause urinary retention in such cases when the obstructing force is still slight. The patients may be treated satisfactorily by removal of the obstructing force, provided some sensation remains and the expulsive power of the bladder can first be restored. Expulsive force may be restored in most instances by rest of the detrusor urinae (intermittent or continuous catheterization for mild dysfunction and suprapubic cystostomy for more advanced disorders) and drug therapy (pilocarpine or mecholyl). When this is done, prostatic massage, urethral dilatation and transurethral resection may be employed to relieve the obstruction. Education is important in insuring continued emptying of the bladder postoperatively; this should consist of teaching the patient to micturate at regular intervals, in a leisurely manner, by using the sitting position, manual pressure and a series of voluntary efforts. Atrophy of the detrusor urinae which is so severe as to prevent restoration of contractility, almost complete loss of sensation and mental deterioration will defeat these measures and contraindicate their employment. Nine instances of successful application of these methods and 3 of failure were reported.

PROSTATE GLAND

Arterial Distribution.—Flocks [50] described the distribution of arteries within the prostate gland in the infant prostate, the normal adult prostate, the prostate showing hyperplasia, the carcinomatous prostate and the prostate after transurethral resection.

There are two groups of arteries within the prostate gland: the capsular group, which show little change with age and with the occurrence of hyperplasia, and the urethral group, which enlarge significantly with age and markedly when hyperplasia is present. The latter group is important in the consideration of transurethral prostatic resection and local repair after this operation, for two reasons: (1) In its anatomic arrangement the urethral group of arteries penetrates at the prostatic vesical junction and then turns distally in a course more or less parallel to the urethral surface, and (2) in its ultimate destination this group of arteries forms the main source of blood supply to the hypertrophied portion of the prostate gland.

Genesis of Hypertrophy.—In conformity with the studies of Reischauer and Grassmann, Pollak [51] found multiple parenchymatous foci in the periurethral prostatic tissue in many cases of early prostatic

50. Flocks, R. H.: The Arterial Distribution Within the Prostate Gland: Its Rôle in Transurethral Prostatic Resection, J. Urol. **37**:524-548 (April) 1937.

51. Pollak, Walther: Zur Genese der Prostatahypertrophie, Ztschr. f. Urol. **31**:49-67 (Feb.) 1937.

hypertrophy. These foci may later become fibromuscular nodules. At the same time numerous nodules are forming in the periurethral glands. In practically all cases of advanced prostatic hypertrophy a growth of the epithelial and mesenchymal parts of the organ is found. Everything points to the fact that hypertrophy is a change which occurs in every old prostate gland but causes clinical symptoms in only a few. Prostatic hypertrophy is caused by a decrease in the formation of androgen, setting free heterosexual influences which had been restrained up to that moment. The term "prostatic hypertrophy" best describes the changes found and should not be altered for another more modern term.

Resection.—In order to obtain data for a report which covered 27,000 transurethral prostatic resections, Chetwood [52] sent questionnaires to 800 members of the American Urological Association.

Nine hundred and eighty-six deaths were reported; no cause was given for 822, but the causes were probably divided between hemorrhage and infection, which constituted the largest number of causes reported. Other causes named were perforation of the bladder, rupture of the bladder, embolism, pyonephrosis and explosion during operation.

The most common complications reported by 98 per cent of the operators (none reported by 2 per cent) were hemorrhage, varying from that of a controllable degree to that requiring suprapubic cystotomy, and infection, local and general, varying from mild pyuria to perivesical cellulitis and gangrene and occasionally septicemia. Other complications enumerated were urinary extravasation, pyelitis, pyelonephritis, uremia, thrombosis, chronic urethral cystitis, stricture, incontinence and epididymitis.

Respecting the percentage of cases in which transurethral prostatic resection is adaptable: Chetwood found that it was variously claimed to be from 75 to 98 per cent and even 100 per cent. Seventy-five per cent would be a notable achievement, 98 per cent would be doubtful, and if it was 100 per cent the operation would be a panacea, which it is not.

Emmett,[53] in discussing relief of postprostatectomy vesical dysfunction, stated that two main classes of patients are recognized: those who have never been relieved by prostatectomy and who seek relief within three years after the operation and those who have experienced complete relief for many years but who finally suffer from a recurrence of obstruction, either with recurrence of benign hyperplasia or with the formation of carcinoma after the original operation had been per-

52. Chetwood, C. H.: Summary of Over Twenty-Seven Thousand Cases of Transurethral Prostatic Resections, Tr. Am. A. Genito-Urin. Surgeons **29**:213-217 (May) 1936.

53. Emmett, J. L.: Relief of Post-Prostatectomy Vesical Dysfuction by Transurethral Surgery, J. Urol. **37**:569-581 (April) 1937.

formed for benign hyperplasia. The latter group demonstrates the fact that prostatic hyperplasia does recur and also that total prostatectomy is no insurance against the formation of prostatic carcinoma.

Sixty-seven cases were reported in which transurethral prostatic resection was necessary subsequent to prostatectomy in order to control symptoms. Forty-two of the patients underwent resection three years after prostatectomy, and half of them, in addition to having marked symptoms of obstruction, were suffering from a persistent suprapubic sinus.

The three most common types of obstruction found were obstruction due to a cicatricial, deformed prostatic urethra and neck of the bladder, that due to remaining prostatic tissue and that due to carcinoma. An extremely high percentage of patients may be relieved of their symptoms by transurethral prostatic resection.

Bumpus and Massey [54] reviewed 71 cases from private practice in which prostatic obstruction was treated by transurethral resection; in 80 per cent of the cases there was no preliminary preparation. Thirty-eight per cent of the patients were more than 70 years of age. The average period of hospitalization was less than one week. There was 1 death. This same trend in the abandonment of preliminary treatment in resection is borne out at the Mayo Clinic, where during 1935, 765 resections were done with but 7 deaths; 65.7 per cent of the patients received no form of preliminary drainage.

In the series of cases at the Mayo Clinic but 3.9 per cent of the patients received suprapubic drainage prior to resection during 1935. Alcock had used it in only 30 of his 1,400 resections, an incidence of 2.1 per cent, while Bumpus and Massey had employed it in 16 per cent of their resections. Thirteen patients, or 18.1 per cent, were subjected to suprapubic cystostomy. The average age of these patients was 71 years. An average of 26.8 Gm. of tissue was removed, and the total time spent in the hospital for cystostomy and resections averaged twelve and a half days per patient.

Negley [55] submitted two tables containing data on patients from Los Angeles and vicinity. In these tables he contrasted the surgical procedures, preoperative preparation, complications, stay in the hospital and mortality in cases in which prostatectomy was performed with those in which resection was performed. He listed charity patients in table 1 and private patients in table 2.

Table 1, which is a résumé of the work of approximately 30 urologists, would seem to show that all of them still prefer some sort

54. Bumpus, H. C., Jr., and Massey, B. D.: Transurethral Resection: Does It Require as Exacting a Preoperative Preparation as Prostatectomy? California & West. Med. **46**:89-91 (Feb.) 1937.

55. Negley, J. C., in discussion on Bumpus and Massey,[54] p. 92.

of preliminary drainage in all cases in which prostatectomy is performed and in 78 per cent of those in which resection is done. There was a difference of only five days in the preoperative preparation in favor of resection. Prostatitis was a complicating factor in only 50 per cent of cases. Complete retention in almost five times as many cases in which prostatectomy was performed as in those in which resection was done would seem to compel more pretentious preparation in the former. Another reason why a patient who is to undergo resection needs less preparation is that in many cases resection is done for relief of symptoms rather than because of large amounts of residual urine. Deaths following resection outnumbered those following prostatectomy in the proportion of 2 to 1, but most of the deaths from resection were the result of surgical accidents.

Table 2 presents a résumé of the records from a large private hospital; it represents the work of general surgeons as well as urologists and would seem to show that there is a difference of only eight days in the preoperative preparation in favor of resection. Again the untoward results of an indwelling catheter were present in only 8 per cent of cases in which combined methods were used. The fact that complete retention was more frequent (2:1) in cases in which prostatectomy was performed would seem to necessitate longer preparation in such cases. Deaths from resection outnumbered those from prostatectomy 6 to 1; 75 per cent of them were due to pyelonephritis and uremia. The most important factor bearing on preoperative preparation is that 73 per cent of the patients who had resection entered the hospital only one day prior to operation; 75 per cent of the deaths occurred in this group. Surely, this shows that preoperative preparation might have helped.

In conclusion, Negley stated that any group of patients 65 years or more of age, many of whom have myocardial disease, renal disease, prostatitis and infected urine, cannot be standardized but must be treated individually, both as to preparation for operation and as to the type of operation. Certainly, one who has reached the "prostatic age" is entitled to a rest in bed for a week or more before operation is done, as a reward, if for nothing else.

Blatt [56] discussed the cases of obstruction of the neck of the bladder observed at the Rubritius Clinic during the last fifteen years. He accepted Marion's classification, which divides the diseases of the neck of the bladder into three groups: contracture of the neck, hypertrophy of the sphincter and glandular hypertrophy of the neck. Blatt stated

56. Blatt, Paul: Die Sphincterkeilexcision bei den Erkrankungen des Blasenhalses (Sphincterhypertonien und Spincterscleroseu), Ztschr. f. urol. Chir. u. Gynäk. **42**:31-47 (Dec.) 1936.

that the third group consists of small adenomas of the prostate, which are often difficult to see, even during operation. This condition was formerly called atrophy of the prostate. The author observed 15 cases of hypertrophy of the sphincter; the patients were all treated by cuneiform excision of the sphincter through a suprapubic incision, with good success. There were 13 cases of contracture of the neck of the bladder; the patients were treated by cuneiform excision. The results were successful in 12 cases, but 1 patient died of ascending infection of the kidneys.

Postoperative Mortality.—Rolnick and Riskind [57] reviewed the records of the Cook County Hospital for the past five years. The review included a series of 897 cases in which the following operations were performed: cystotomy, cystotomy and suprapubic prostatectomy, perineal prostatectomy, cystotomy and resection and transurethral resection. They were impressed by the fact that there has been a noticeable lowering of mortality among their patients. Previous to the era of resection, two stage prostatectomy had been the routine procedure. With the advent of resection, they were impressed with its value but learned soon that it would not be wise to adopt resection as a routine operation, as had previously been the case with two stage suprapubic prostatectomy. Within the last two or three years the patients have been selected as to their suitability for suprapubic, perineal or transurethral attack, and as a result there has been a lower mortality. The statistics from the Cook County Hospital for 1935 show that of 237 patients operated on, 50 (21 per cent) died. This includes those subjected to all types of operation, including cystotomy. Resection was performed in 110 cases, with 16 deaths (14.5 per cent). In 25 cases in which two stage suprapubic prostatectomy was performed 6 (24 per cent) of the patients died, and in 36 cases in which perineal prostatectomy was performed 4 (11 per cent) of the patients died. It can thus be readily seen that resection has been the largest factor in lowering mortality in some cases in which the patients are poor risks.

Rolnick and Riskind concluded that careful selection of cases and the use of all the routes for attack on the prostate glands have been factors in lowering the mortality. If intolerance to the catheter or marked infection is present, a preliminary cystotomy should be done. Cystotomy, done carefully and under local anesthesia, carries with it practically no mortality. Two stage suprapubic prostatectomy is a satisfactory procedure and carries with it a low mortality in those cases in which the patients can be considered only fair risks. Transurethral resection is the safest procedure for the patient who is a poor

57. Rolnick, H. C., and Riskind, L. A.: Mortality in Prostatic Surgery, J. Urol. **37**:12-17 (Jan.) 1937.

risk and who does not have a large prostate. Cystotomy followed by resection has little or no mortality and is the safest of all procedures for attack on the prostate gland. A patient who is a good risk for a one stage operation or in whom carcinoma is suspected should be subjected to perineal prostatectomy. The high incidence of occult carcinoma of the prostate gland should be considered seriously in determining the type of operation.

Carcinoma.—In 1935 Bugbee [58] reviewed cases of carcinoma of the prostate which he had observed over a period of twenty-five years. He concluded that in dealing with carcinoma of the prostate gland one is dealing with an essentially fatal disease and that occasional enthusiastic reports of results obtained in isolated series of cases are either immediate results obtained by a certain method of treatment or they represent results obtained in a group of cases in which the patients would react favorably to any method of procedure; the patients have the type of carcinoma, in fact, that would probably grow slowly were no specific treatment employed.

Since 1932 Bugbee has performed 63 resections on 52 patients; there was no operative mortality, but 12 patients died later. Forty patients were alive and had had satisfactory vesical function when last heard from, which was from one month to four years after resection. No radium was employed in any of these cases, and high voltage roentgen therapy was employed only in an attempt to control hemorrhage before operation. In no case did the growth recede under roentgen therapy, and in 2 cases the urinary symptoms were aggravated.

In every case of carcinoma of the prostate with retention observed during a four year period, whether metastasis was present or not, resection had been carried out and urinary function restored. In every case it was possible to pass the resectoscope after sufficient dilation of the urethra. With the orifice well freed of the encroaching growth, it had remained open, certainly for an appreciable length of time; up to the time this paper was written only 3 patients had required reoperation—1 for severe hemorrhage, which was controlled by another resection, and the other 2 for a marked increase in the size of the remaining growth. Nine of the first patients who were subjected to resection required a second resection before they left the hospital. The amount of tissue removed varied from 4 to 56 Gm.

There seems to be less shock associated with resection for carcinoma than with resection for hypertrophy. With the reestablishment of vesical function and the ability of the patient to empty the bladder, tenesmus, dysuria, local congestion and infection subside. If pain has

58. Bugbee, H. G.: Experiences with Transurethral Resection in Carcinoma of the Prostate, Tr. Am. A. Genito-Urin. Surgeons **29**:207-212 (May) 1936.

been present in the perineum and legs, this usually diminishes. In 6 instances, a tumor of the bladder, either adjacent to or independent of the carcinoma of the prostate, was removed by resection at the same time as the prostatic resection. In no instance did the growth appear to be stimulated by the resection or was local or metastatic extension accelerated, as has been suggested by some writers.

In comparing the results to be obtained with open operation, resection or irradiation, one must realize that circumscribed growths, which often grow slowly, may respond favorably to any form of treatment or do well for a considerable time when left alone, while resection and often irradiation are employed for all types of carcinoma associated with retention, most often for growth in the advanced stage, which would not be considered as suitable for a radical prostatectomy.

Hager and Hoffmann [59] summarized the findings in 396 cases of malignant conditions of the prostate observed at the Los Angeles General Hospital in thirteen years. There were 240 deaths in the series, 186 of which occurred within the first year. Fifty-four patients lived from one to ten years, but few survived for three years. Sixty were reported as living. The authors were unable to trace 89 of the patients.

The scope of treatment in general has been conservative, with the institution of those measures necessary for the relief of urinary obstruction. The subject of metastasis is paramount in the choice and limitation of treatment and also in prognosis. It is probably the deciding factor in the determination of relative cures. Metastasis was demonstrated by roentgenograms at the initial examination in 107 cases and after the first examination in 26 instances, in a period of five years. It is apparent that in fully 25 per cent of cases there was demonstrable metastasis to bone at the time the diagnosis was first made.

Graves, Warren and Harris [60] studied 7 cases of carcinoma of the prostate and 1 case of carcinoma of the bladder by the use of large sections made through the soft tissues and adjacent bones of the pelvis. Perineural lymphatic involvement was a constant feature in the cases of carcinoma of the prostate, but was absent in the case of carcinoma of the bladder. Owing to the abundant nerve supply in and about the prostate gland, opportunity for perineural lymphatic involvement is great. The pain associated with prostatic cancer is clinical evidence of the existence of perineural involvement. While hematogenous metastasis may occur in carcinoma of the prostate, the chief factors in the marked preponder-

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59. Hager, B. H., and Hoffmann, E. F.: Statistical Data on Three Hundred and Ninety-Six Cases of Carcinoma of the Prostate, J. Urol. **37**:180-185 (Jan.) 1937.

60. Graves, R. C.; Warren, Shields, and Harris, P. N.: Osseous Metastases of Carcinoma of the Prostate with Special Reference to the Perineural Lymphatics, Tr. Am. A. Genito-Urin. Surgeons **29**:179-205 (May) 1936.

ance of metastatic lesions in the pelvis and in the lower portion of the spinal column are the distribution of the nerves and the conduction of tumor along the perineural lymphatics into close contact with the bone. Many metastases occur as a direct invasion of the marrow spaces through the cortical ostia. Early metastases may be missed in roentgenographic study. Conversely, under rare conditions metastases may be erroneously diagnosed, and there actually may be only an irregularity in the extent of resorption of bone. Invasion of the lymphatic channels is a frequent occurrence, and metastases through the usual lymphatic route is an important method in which the disease spreads, although probably this is not a factor in determining the localization of the bony metastases. The perineural lymphatic dissemination of the tumor may be either by continuity or by embolism. Involvement of soft parts, particularly the rectum, seminal vesicles, vas deferens and ureters, can be readily studied by this method.

Nitch [61] stated that the results of radical operations for carcinoma of the prostate gland have been so disappointing in other than Young's hands that he confines his treatment to conservative or palliative measures consisting of high voltage roentgen therapy, radium therapy, suprapubic drainage, transplantation of the ureters, electroresection or a combination of any of these, as indicated.

As far as high voltage roentgen therapy is concerned, the immediate results are sometimes remarkable, but the ultimate results are disappointing. Some of the severe reactions, such as cystitis, ulcerative proctitis and lymphedema, can be obviated by the split dose method of Levitt, but the best that can be hoped for is a remission of the symptoms for an average of one and a half years.

Nitch used radium in massive doses. Six or eight platinum needles, each of which contains 1 mg. of radium, are placed in the prostate gland through a Young perineal incision. Two needles, each of which contains 3 mg. of radium, are placed in the connective tissue on each side of the prostate gland. The bladder is opened, and a metal box containing 50 mg. of radium is placed on the vesical surface of the prostate. Five milligrams of radium is then placed in the posterior urethra, in a rubber tube attached to a Pilcher bag which surrounds the metal box. The box and the urethral tube are removed in twenty-four hours, and the platinum needles are removed in ten days. Nitch stated that the results of the treatments have been encouraging but by no means startling.

Of the surgical measures, transurethral electroresection is the best for relief of obstruction if the caliber of the posterior urethra permits

61. Nitch, C. A. R.: The Conservative Treatment of Carcinoma of the Prostate, Brit. J. Urol. **8**:329-336 (Dec.) 1936.

its use. It is contraindicated in the presence of a rapidly growing carcinoma, as relief is of such short duration that suprapubic drainage is a better procedure. Nitch has employed transplantation of the ureters to the intestine in 2 cases but stated that it can be performed only in carefully selected cases. He concluded that in the future electroresection followed by some form of radiotherapy will be the method of choice.

Young [62] reported that recent statistics showed that carcinoma of the prostate occurs in at least 14 per cent of men past 44 years of age. Carcinoma of the prostate is three times as common as that of any other internal organ. In half of the cases this lesion is associated with prostatic hypertrophy. The two lesions are distinct in their origin. In a large percentage of the cases, carcinoma begins in the posterior lobe of the prostate gland, where it is easily palpable by rectum. An area of marked induration should arouse suspicion. A positive diagnosis can be made without danger, by exposure of the growth through the perineum.

If the cancerous nodule is small, it may be radically removed by hemiprostatovesiculectomy. If the growth is more extensive, Young's radical operation has been shown to result in a complete cure in more than 50 per cent of the patients operated on. Many early carcinomas of the prostate gland would be discovered if rectal examination were made during physical examinations on men past 40 years of age. Young stated that the radical operation for carcinoma of the prostate is not difficult and that the mortality is low. Normal micturition and complete urinary control have been obtained in many cases. In those cases in which the patients were not cured but died later of metastasis, the local result was often satisfactory. Young was of the opinion that the perineal route affords the only adequate approach for confirmation of the diagnosis of carcinoma of the prostate and its radical cure. In the presence of benign growths it gives the best results and the mortality is as low as for any other procedure if the patient is observed for a month after operation.

Tuberculosis.—Moore [63] found tuberculosis of the prostate in 20 (12.3 per cent) of 163 cases of tuberculosis. The gross appearance is that of an irregular yellow or grayish yellow homogeneous or finely granular, rubbery or crumbly focus in the peripheral parts of the posterior and lateral lobes. It should be distinguished from carcinoma and dilated acini filled with lipoid-rich inspissated secretion. The lesions are typically caseous. It seems most probable that the bacilli in most

62. Young, H. H.: The Radical Cure of Cancer of the Prostate, Surg., Gynec. & Obst. **64**:472-484 (Feb.) 1937.

63. Moore, R. A.: Tuberculosis of the Prostate Gland, J. Urol. **37**:372-384 (March) 1937.

cases reach the prostate gland through the blood stream and first invade the periacinal tissue and acinal lumens. There is histologic or correlative evidence that the prostatic lesion is secondary to other urogenital tuberculosis in less than 20 per cent of the cases.

URETHRA

Anatomy.—From a comparison of the urethras and necks of the bladders from 30 women with those from 17 girls 4 years of age and younger, MacKenzie and Beck [64] concluded:

1. Chronic inflammation of the urethra and bladder neck is present in a higher percentage of adults than we have heretofore imagined.

2. Perimucosal structures about the bladder neck and posterior third of the urethra are acquired.

3. These acquired structures simulate prostatic tissue because they take origin from the same type of embryologic tissue, and thus have the same inherent properties.

4. The stimulus required for the acquisition of these structures may be: (*a*) infection within the genito-urinary tract, (*b*) structural anomalies within the genito-urinary tract or (*c*) trauma of childbirth.

5. These buds and nests known as von Brunn cell nests or buds, in so far as they are a proliferation of the mucosal epithelium, develop their lumen from the intra-epithelial glands as seen in the mucosal epithelium in children.

6. Those structures about the bladder neck and posterior urethra referred to by previous workers as prostatic structures, we consider to result from a process similar to cystic disease of the upper genito-urinary tract, better known as pyelitis cystica, ureteritis cystica, and cystitis cystica, according to location. We propose to call it cystitis cystica about the bladder neck, and urethritis cystica when it occurs in the urethra.

Tumor.—Dózsa [65] discussed the primary tumors of the female urethra. Of the benign tumors, the most frequent are caruncles, which histologically can be divided into three groups: granuloma, papillary angioma and telangiectasia. Fibroma, fibromyoma and myoma are rare. The common malignant tumor of the urethra is the carcinoma. Sarcoma is rare, and its histologic structure varies greatly. The symptoms of urethral tumor depend on the nature, the size, the position and other peculiarities of the growth. Often symptoms of trigonitis, cystitis and urinary infection complicate the clinical picture. The diagnosis is usually easy to make. Biopsy and urethroscopy are sometimes required. Differential diagnosis has to include rodent ulcer, primary sclerosis and tuberculous ulcer. Treatment of a benign tumor is simple

64. MacKenzie, D. W., and Beck, Sidney: A Histopathologic Study of the Female Bladder Neck and Urethra, Tr. Am. A. Genito-Urin. Surgeons **29**:227-253 (May) 1936.

65. Dózsa, Eugen: Ueber die Neubildungen der weiblichen Harnröhre, Ztschr. f. urol. Chir. u. Gynäk. **42**:381-395 (Dec.) 1936.

and consists of excision or coagulation; the prognosis is good. Prognosis of the malignant tumor is bad; treatment can effect a lasting cure only when the growth is in the early stage. A carcinoma usually responds well to radium treatment but not so well to roentgen therapy. Most urologists prefer to combine irradiation with surgical removal. The urinary stream must usually be deviated before extensive surgical removal of the tumor is performed, either by suprapubic drainage or by transplantation of the ureters into the bowel. Some surgeons, among them Marion, use a plastic procedure to form a new urethra after resection and close the suprapubic fistula.

Trauma.—Beach [66] offered the following generalizations regarding the management of the so-called "straddle" injury, based on his experience with 16 cases: Every patient who has a rupture of the urethra, whether partial or complete, should be hospitalized. This is particularly so in cases in which the patient voids spontaneously after the accident; such injuries are the most difficult to handle, and complications develop readily. Many partial ruptures, when catheterization is possible, respond satisfactorily, and no complications develop when an indwelling catheter is used. If catheterization is impossible, operation must be undertaken immediately. The most satisfactory results are obtained by surgical treatment, which should be bold, direct and as simple as possible. Operation must not be too extensive at any one time. It is better only to drain the bladder at first. After a few days of rest, subsequent operation may be carried out with comparative ease.

Simpson-Smith [67] reported 8 cases of rupture of the urethra, each of which furnished some separate point for discussion or improvement in management. In addition, he reviewed all the available cases which had been reported in the past twenty years (approximately 381 cases), in order to present a reliable picture and to measure the trend of modern urologic views.

The site of the rupture was as follows: the bulbous portion of the urethra in 50 per cent, the membranous portion in 40 per cent and the pendulous portion in 5 per cent of the cases and the female urethra in 2 per cent of the cases. In 3 per cent of the cases the site of rupture was not stated. Forty-six per cent of the ruptures were caused by falls, usually with the patient astride some object; 5 per cent were caused by blows, and 3 per cent followed instrumentation of the urethra.

The type of urethral rupture depends on the degree of injury. In partial ruptures either the mucous membrane alone is torn, as in penile

66. Beach, E. W.: The So-Called "Straddle" Injury: Its Management, California & West. Med. **46**:234-239 (April) 1937.

67. Simpson-Smith, A.: Traumatic Rupture of the Urethra: Eight Personal Cases, with a Review of Three Hundred and Eighty-One Recorded Ruptures, Brit. J. Surg. **24**:309-332 (Oct.) 1936.

injuries, or, more commonly, part of the urethral wall may be split. In complete ruptures a blow sufficient to sever the tough urethra usually causes much crushing of the ends, and the gap thus formed is further increased by the retraction of the elastic tissue. "Complete fracture" of the urethra arises as a result of severe perineal laceration by a blunt instrument.

The symptoms of traumatic rupture are few and straightforward; they readily lead to a correct diagnosis. Shock, pain, bleeding from the penis, perineal hematoma and ecchymosis, abnormality of micturition and occasional extravasation are the principal symptoms. Shock is severe, even when the extreme end of the penis alone is injured.

The passage of a catheter is the most unreliable means of diagnosis and should not be employed. There are no less than 42 cited instances in which diagnostic catheterization was unsuccessful. In only 6 cases was this procedure definitely forbidden.

A general analysis of the treatment employed disclosed that the perineum was incised in no less than 248 cases, and the bladder was opened in only 181. In only a few of these 181 cases was the bladder definitely recorded as closed at the end of the operation, and so 181 represents the maximum of urinary deviation, that is, just less than 50 per cent. The indwelling catheter was used 180 times. In 105 cases it was employed as a splint to insure the patency of the urethra, for a temporary suprapubic tube drew off the urine; in the remaining 75 cases the catheter alone served the dual purpose of splint and drain. Perineal section was done in 248 cases, and end to end anastomosis was performed in 141 cases. An indwelling urethral catheter was used in 180 cases; the membranous portion of the urethra was injured in 92 of these, the bulbous portion in 83, the penile portion in 2 and the female urethra in 3. Drainage of the perineal wound was employed in 41 cases, and suprapubic drainage of urine was used in 181 cases. The urethral ends were stitched to perineal skin in 16 cases.

In all cases success will depend on the following factors: admission of the patient to a hospital as soon as possible after the accident has occurred and before micturition has been allowed; a careful toilet of any proposed operative site, particularly of the perineum, penis and anterior portion of the urethra; prompt diversion of the urinary stream by a suprapubic incision, if necessary, with use of a local anesthetic; retrogression of a "boiled" gum elastic catheter down the urethra to establish a diagnosis of partial or complete rupture, and discarding of this catheter, if it can be passed, from the meatal rather than the vesical end; wrapping of the penis in a sterile dressing which cannot fall off, to prevent ascending infection during the healing stage, and high elevation of the foot of the bed (allowing several pillows under

the head for comfort), to insure that the urine will flow away from the meatus into the fundus of the bladder.

Treatment is urged as soon as possible after the accident and is directed against fouling of the raw area by urine, haphazard catheterization or perineal contamination. Suprapubic deviation is submitted as essential in the treatment of all ruptures, partial or complete. The only exception to this rule is the rare injury to the penile shaft. An indwelling catheter is said to be well tolerated in cases of rupture of the posterior or "membranous" portion of the urethra, and in only a few cases does it produce strictures or necessitate perineal exploration. Rupture of the bulbar portion is certainly prone to the formation of stricture. In the presence of such a lesion suprapubic cystotomy is instantly performed, but an external urethrotomy is postponed until the bruised tissue has recovered, until the necrotic tissue is well differentiated and until accurate end to end suture approximation has a better chance of "holding" and healing. A penile injury is of less serious moment and may not require a suprapubic operation. Injury of the female urethra requires immediate diversion of the urinary stream.

Urethral Glands.—Cabot and Shoemaker [68] discussed the rôle of glands of the female urethra in the production of infection of the urinary tract. This study of a fair amount of material seems to warrant the following deductions:

There is no evidence of true glands in the proximal two thirds of the female urethra. Two specimens were found to contain areas of secretory epithelium in the mucous membrane, but this did not extend into the submucosa. The structures referred to as corpora amylacea by Renner are not specific products of the prostate gland. To refer to them as evidence of glandular structures homologous to the prostate gland simply confuses the issue. The colloid-containing cysts in the urethral mucosa and submucosa are formed from von Brunn's cell nests. The mechanism of their formation is the same as that of the colloid-containing cysts elsewhere in the urinary tract. They may properly be designated as urethritis cystica.

Returning to the question suggested by the title of their paper, namely, the relation of the glandular structures to infection of the urinary tract in the female, Cabot and Shoemaker disagreed with the position taken by Renner, Folsom and others. Their view that glandular structures are the basis of infection does not seem tenable. Their position is further weakened by the well known behavior of the urethra when infected by the gonococcus. This type of infection commonly

68. Cabot, Hugh, and Shoemaker, Rosemary: The Rôle of Glands of the Female Urethra in the Production of Infection of the Urinary Tract, Tr. Am. A. Genito-Urin. Surgeons **29**:461-472 (May) 1936.

runs a mild course and goes on to recovery, except when it is complicated by involvement of Skene's or of Bartholin's glands. These glands are generally accepted as homologous respectively to the prostatic glands and the glands of Cowper. But Skene's glands lie in the distal third of the urethra and are out of the field of the present discussion. The glands of Bartholin obviously do not enter at all. Now if there were important glandular masses in the proximal two thirds of the urethra, they would certainly become involved and prolong the inflammatory process. Experience suggests that this does not occur.

Looked at from another point of view, inflammation of the urinary tract of the so-called ascending type is notoriously common among female children. These infections are assumed to reach the bladder through the urethra and might properly be expected to invade glandular masses in the proximal portion of the urethra if such existed. As far as is known, chronic posterior urethritis in children is not believed to be a common lesion. Finally, it is notorious that the lesions of the female urethra, to which reference was made at the beginning of this paper, are characterized by normal or substantially normal urine. This speaks against a glandular origin, not for it.

SEMINAL VESICLES

Tuberculosis.—Chauvin [69] stated that the diagnosis of primary tuberculosis of the seminal vesicles may present itself under two variable aspects. The signs may, on the one hand, consist more or less clearly of a refractory urethral discharge, chronic from the start, with moderate pollakiuria or terminal hematuria, which will point toward a lesion of the urogenital level, urethral, prostatic or vesicular, as the case may be. Or, on the other hand, the patient may have no genital symptoms but distinct urinary symptoms which suggest that he is suffering from renal tuberculosis. In this case pollakiuria and slight terminal hematuria, accompanied with pyuria and albuminuria, will in part point toward vesicorenal lesions. In cases in which the urine contains pus, albumin and Koch bacilli, the nature of the lesion is easy to determine; it is its localization that is difficult. Negative findings when the ureters are catheterized and negative results of inoculation will demonstrate that the kidneys are not the site of infection. As it is generally agreed that there is no such thing as primary tuberculosis of the bladder, there are left only the prostate gland and the seminal vesicles as the source of the pus and bacilli. Rectal examination and massage of the prostate gland and seminal vesicles will reveal the state of these organs and assist in diagnosis. But one should still be cautious in making a

69. Chauvin, E.: La tuberculose primitive des vésicules séminales, Arch. d. mal. d. reins **10**:63 (Jan.); 129 (March) 1936.

diagnosis of primary tuberculous vesiculitis and remember that there are renal lesions which remain silent for a long time and which only prolonged observation can exclude.

In prognosis, when the foci in the seminal vesicles break their bounds, it is usually to the prostate that the tuberculous process extends in an attempt to find its way out into the urethra through a softened prostatic focus. Primary vesiculitis constitutes an initial stage of tuberculous invasion of the urogenital apparatus. All its gravity lies in its possibilities of generalization. Chauvin has never seen renal tuberculosis occur secondary to tuberculosis of the seminal vesicles, but a downward extension from these organs into the genital tract is frequent. Experience has proved that tuberculous lesions of the seminal vesicles occasionally may pass into encystment and disappear, ending in complete cure.

It is agreed that no localized tuberculous process can be cured unless appropriate medical treatment is directed to the modification of the general condition. Such types of treatment as physical therapy, hyperpyrexia and ultraviolet therapy have all been used with some success.

Local treatment must be given with great caution. Massage is liable to spread the infection toward the testes and to cause general septicemia.

Surgical extirpation of the tuberculous lesion, while it seems at first glance to constitute an ideal method of treatment, has not, to Chauvin's knowledge, been carried out, unless exceptionally. He pointed out that vesiculectomy is not so radical an operation as it appears; fine prostatic granules may be left behind unperceived, as may beginning lesions and funiculitis and of the vas deferens. He regarded vesiculectomy as a difficult and grave operation, regardless of the route chosen. He stated that in an immense majority of cases the surgeons who have attempted it have had to be content with atypical and partial resections, always incomplete, or sometimes with simple curettage. Even if these operations may give satisfactory results in the treatment of inflammatory lesions, which are opened and drained widely, they should not be used for a tuberculous disease, since the only conditions under which surgical treatment is permissible are those in which one can be absolutely sure of removing the tuberculous lesion in its totality. This makes it highly important that tuberculous vesiculitis be correctly diagnosed in its earliest stages.

Carcinoma.—McNally and Cochems [70] stated that 16 instances of primary carcinoma of the seminal vesicles have been reported in the

70. McNally, Andrew, and Cochems, F. M.: Primary Carcinoma of the Seminal Vesicles, J. Urol. **36**:532-537 (Nov.) 1936.

literature, of which only 4 were definitely proved. In the case reported by these authors, the chief complaint was hematuria. The diagnosis of primary carcinoma of the right seminal vesicle was made on the basis of hematuria and a hard mass in the right seminal vesicle. The tissues were radically excised, and the clinical diagnosis was confirmed by the histologic examination of the tissue removed. The prostate gland was later removed and found to be free from carcinoma. An additional interesting histologic observation was the presence of tuberculosis. In the excised prostatic tissues were lesions of tuberculosis, apparently a latent activated infection associated with an old tuberculosis of the spinal column. The patient is free from clinical evidence of recurrence or metastasis more than two years after operation. This seems to be the only case of primary carcinoma of the seminal vesicle on record in which the patient was alive and free from symptoms two years after radical excision.

TESTES

Undescended Testes.—Hess, Kunstadter and Saphir [71] stated that the determination of the gonadotropic hormone in the urine of 13 boys who had cryptorchidism revealed the presence of significant amounts of the hormone in the urine of 5. These data are consistent with the belief that in the latter cases the condition resulted from a failure of the gonadal mechanism, the pituitary body being functionally active. The patients responded to treatment with gonadotropic substance by descent of the testes and disappearance of the hormone from the urine.

In 3 cases of unilateral cryptorchidism in which the descended testis was apparently normal there was no increase in the excretion of gonadotropic hormone prior to treatment, and only 1 of the 3 patients responded to treatment by descent of the other testis.

In 2 of the 5 cases of bilateral cryptorchidism in which there was no gonadotropic hormone before treatment and in which treatment with gonadotropic substance was not successful, primary pituitary dysfunction was diagnosed, as there was clinical evidence of infantilism in each case.

The authors were of the opinion that if the results in their series of cases are substantiated by future observations there is indication of a possible sphere of usefulness for the determination of the urinary gonadotropic hormone in expressing the prognosis in case of cryptorchidism in which treatment is being given. The presence of the hormone in the urine justifies medical treatment and offers a favorable prognosis in the absence of mechanical obstruction.

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71. Hess, J. H.; Kunstadter, R. H., and Saphir, William: Urinary Excretion of Gonadotropic Hormone in Cryptorchidism, J. A. M. A. **108**:352-354 (Jan. 30) 1937.

TUNICA VAGINALIS

Hydrocele.—In 23 cases in which there were 25 hydroceles a cure was obtained in all except 1 case.[72] The patients were followed from one to forty-eight months, the average period being seventeen and three-tenths months. There were 2 examples of bilateral hydroceles, with complete cure in each case. The smallest hydrocele had a capacity of 5 cc. and the largest 1,400 cc.; the average capacity in cases in which a cure was obtained was 187 cc., which should be an indication that size is no contraindication to this type of therapy. The youngest patient was 6 years of age, and the oldest was 77 years; the average age in the cases in which the age was given was 50.4 years. From one to four injections were required; an average of two and four-tenths injections were employed in the cases in which a cure was obtained.

URINE

Anuria.—In an effort to explain the problem of reflex anuria, Uebelhör [73] studied the renorenal reflexes by direct visual observation of the renal capillary system. Changes were observed in rabbits and in guinea-pigs which can be compared with the pathologic process in man. The existing theory that reflex anuria arises in the healthy kidney by a sudden ischemia caused by injury of the other kidney is possible. By chemical examples Uebelhör indicated the variation of the causes of anuria. He reported several cases which support his theory and make the origin of true reflex anuria easier to understand. Often, in cases of so-called reflex anuria, causes other than a reflex mechanism can be found to explain the anuria. The author discussed the morphologic findings in cases of anuria and showed that a careful microscopic examination of the kidneys sometimes may disclose the cause of the condition.

Root [74] stated that anuria may occur in cases in which the patient has only one kidney and be associated with infection of mild degree, especially if a loss of base and chloride occurs as a result of vomiting, sweating or diarrhea. Intravenous administration of physiologic solution of sodium chloride in sufficient quantity may produce relief even after ninety-six hours of anuria. The injection of hypertonic saline solution may be necessary. The use of solutions more concentrated than 10 per cent may cause a chill and is contraindicated. The administration of salt in the form of liquid, such as broth, or as tablets is

72. Mayers, M. M.: Treatment of Hydrocele and Similar Scrotal Cysts by the Injection Method, J. Urol. **37**:308-318 (Feb.) 1937.

73. Uebelhör, Richard: Die reflektorische Anurie, Arch. f. klin. Chir. **187**: 389-413 (Jan.) 1937.

74. Root, H. F.: The Intravenous Administration of Hypertonic Salt Solution for Anuria in Patients with One Kidney, J. A. M. A. **108**:947-949 (March 20) 1937.

to be borne in mind in cases in which water and chloride are being lost during excessive sweating, diarrhea or vomiting.

Amicrobic Pyuria.—Wildbolz [75] stated that cases of amicrobic pyuria have been observed in Europe for a longer period and much more frequently than in the United States and are the object of eager research. Faltin, before the Eighth Congress of the Northern Surgical Society, in Helsingfors, in 1909, was the first to state that he had observed cases of pyuria in which he was unable to find any micro-organisms in the purulent urine, either by microscopic examination or by culture, and in which tuberculosis could be excluded.

Amicrobic pyuria is of great clinical importance. It is easily curable by medication but is often mistaken for tuberculosis of the urinary tract. As a result of such mistakes, nephrectomy has been performed unnecessarily on a number of patients. Therefore, it is important to make the clinical picture of amicrobic pyuria as widely known as possible. There are two types of amicrobic nontuberculous pyuria: a terminal stage of a urinary infection primarily caused by such an organism as Bacterium coli, the staphylococcus or the streptococcus, and primary amicrobic pyuria.

The first form of sterile pyuria is not rare. Its origin may easily be understood by comparison with similar processes elsewhere. Just as gonorrheal urethritis leaves purulent secretion for a long time after all gonococci have disappeared, infection of the upper part of the urinary tract may leave pyuria after all pyogenic bacteria have gone.

The pathogenesis of the second form of sterile pyuria, primary amicrobic pyuria, is not yet clear. Wildbolz has been unable at any time to find bacteria in the purulent sediment by microscopic examination or by culture. Primary amicrobic pyuria usually sets in acutely, with marked vesical symptoms, urinary urgency and tenesmus and painful micturition. There is no fever and no constitutional disturbance. The urine is purulent and generally contains erythrocytes. Sometimes there is sufficient blood in the urine to be noticed by the patient shortly before death. Cystoscopy shows that the vesical mucosa is reddened in patches and discloses ecchymoses and mucopus in the form of stripes or round white necrotic membranes. There is pus in the urine from one or both kidneys on ureteral catheterization. It is characteristic of amicrobic pyuria that in spite of this renal pyuria one never finds a marked decrease in renal function. Amicrobic pyuria usually is observed in young men and rarely in women.

Schaffhauser succeeded in a few cases of typical amicrobic pyuria in growing nonhemolytic streptococci on Rosenow's bouillon; cultures were positive on this medium alone. Growth was slow; colonies were visible only after from three to four days. It is remarkable that this

75. Wildbolz, Hans: On Amicrobic Pyuria, J. Urol. **37**:605-609 (May) 1937.

streptococcus when transferred to the urinary tract of dogs reproduced in them clinical and pathologic changes similar to those of amicrobic pyuria of man.

Wildbolz stated that a few intravenous injections of an arsphenamine will cure amicrobic pyuria promptly, even when the patient has suffered for months and years from pyuria which has resisted all other therapeutic efforts. Usually one or two injections of 0.15 Gm. of neoarsphenamine are enough to obtain a prompt cure.

Urinary Salts.—Among the important factors affecting the solubility of insoluble salts are the degree of acidity and the neutral effect of the neutral salt. Sisk and Toenhart [76] stated that the importance of acidity is more generally recognized than that of the effect of the neutral salt; however, both are important and both may be applied clinically. The solubility of calcium oxalate is not materially affected by the normal range of acidity encountered in urine, but it is appreciably affected by the neutral salts present.

That the solubility of the insoluble salts is affected by the small amount of colloids present in urine has not been demonstrated, and Sisk and Toenhart found no difference in the solubility of calcium oxalate in a solution of urinary colloids as compared with water. That urinary colloids retard precipitation from a supersaturated solution is yet to be established. That the urinary colloids lower the surface tension of the urine has been established. In doing so, it has been suggested that the surface tension of the urine is brought to the same level as that of the normal mucous surfaces of the urinary tract. In maintaining the state of supersaturation of urine until it is voided, the element of time is important. This explains in part at least the association of stasis and stone, even when the urine is normal. Some dyes retard the precipitation of salts from supersaturated solution.

It is certain that precipitation of a compound will not occur unless the solubility of that compound had been exceeded. A knowledge of the factors influencing solubilities in urine is necessary if one hopes to approach the problem of sediment and stone formation in the urinary tract.

UROLOGIC COMPLICATIONS OF CARCINOMA OF THE CERVIX

In a large series of cases of carcinoma of the cervix which Graves, Kickham and Nathanson [77] studied clinically and at necropsy with reference to changes in the upper part of the urinary tract, obstruction

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76. Sisk, I. R., and Toenhart, Otto: Factors Influencing the Solubility of Relatively Insoluble Salts in Urine, J. Urol. **37**:595-603 (April) 1937.

77. Graves, R. C.; Kickham, C. J. E., and Nathanson, I. T.: The Ureteral and Renal Complications of Carcinoma of the Cervix, J. Urol. **36**:618-640 (Dec.) 1936.

of the ureters was encountered in more than 70 per cent. Because of this high incidence of ureteral occlusion, which has been confirmed by other writers on this subject, it is urged that complete urologic investigation be included in the management of this disease. As has been shown, both diagnosis and prognosis will thus be rendered more accurate, and measures of relief may be made available for the pain and distressing symptoms of uremia which so often confront the patient. It was the opinion of the authors that the urologist may find in this difficult problem a new and highly important field of usefulness.

UROLOGIC COMPLICATIONS OF UTERINE AND OVARIAN TUMORS

Morris and Juracsek[78] made a complete urologic examination of 43 females with tumors which originated in the reproductive tract; 76 per cent had symptoms referable to the urinary tract. In 44.2 per cent ureteral dilatation was demonstrable, and in 37 per cent there was dilatation of the renal pelvis. Symptoms referable to the renal region were present in only 50 per cent of the patients in whom hydronephrosis was demonstrated. Sixty per cent of the tumors which did not rise to the level of the umbilicus produced a variable degree of dilatation of the ureters or renal pelvis. Fifty per cent of the tumors which rose above the level of the umbilicus produced dilatation of the ureters or renal pelvis.

HYDATID CYSTS

Imbert,[79] who made a study of the pyelographic images formed by open and closed hydatid cysts of the kidney, stated that in the presence of a closed cyst pyelography may show a normal image, deformation of the pelvis and calices, amputation of the pelvis and calices or displacement of the ureter; in the presence of an open cyst it may reveal the cystic pocket filled with the opaque substance, and it practically always will show some enlargement of the ureter due to passage of daughter cysts and blood clots. The pyelogram may show definite lacunae; there may be clear zones in the midst of opaque regions in the injected pocket.

The hydatid cyst is rather well adapted for diagnosis by pyelography, since this frequently shows the rounded shadow of the cyst compressing some of the calices. Frequently it is desirable to make two roentgenograms, one before and the other after the opaque fluid has displaced the abdominal mass. An open cyst with a calcified adventitia is rather easily recognized in the pyelogram by the regularity of

78. Morris, H. L., and Juracsek, Valeria R.: Involvement of the Upper Part of the Urinary Tract Associated with Uterine and Ovarian Tumors, J. Urol. **37**:582-587 (April) 1937.

79. Imbert, Marc: La pyélographie dans les kystes hydatiques du rein, Arch. d. mal. d. reins **10**:153-165 (March) 1936.

its contours. It is difficult to distinguish between a hydatid cyst and a solitary cyst; in the presence of an open hydatid cyst, the image of the daughter cysts may be decisive for diagnosis. Bilaterality of the deformation will easily eliminate polycystic kidney. The "spider" form of renal tumor is clearly distinguished from the rounded contours of a hydatid cyst.

As regards the location of the cyst, Imbert stated that pyelography gives precise indications. Thus, a hydatid cyst of the upper pole, acting by force of gravitation, lowers the kidney and produces a zigzag kink of the ureter and an amputation of the superior calix. When the cyst is open, the opaque substance fills the cavity, which then assumes the form of a more or less dilated balloon. If the cyst is in the middle third of the kidney, it will cause the middle calix to disappear, will compress the pelvis and will stretch out the superior and inferior calices and produce a "crescent" appearance. If it is at the lower pole, it will displace the kidney upward and force the ureter to take a regularly rounded curve following the outline of the cyst; this can be recognized in either the frontal or the profile position. The renal pelvis may then become a horizontal line; the inferior calix is frequently amputated, and the compression provokes a hydronephrosis.

Pyelography is thus a guide to the correct mode of operative approach and enables the surgeon to choose a route that will prevent unnecessary destruction of renal parenchyma. For a cyst of the upper pole the lumbar incision should always be employed, since it permits adequate operative exposure, especially after resection of the twelfth rib. This method is also applicable for a cyst of the middle third of the kidney or even for a cyst of the lower pole if the extension is into the abdominal cavity. Pyelography also will indicate whether or not the operation should be conservative. The author cannot agree with Racic, who said that pyelography does not permit a diagnosis more than once in 13 cases. Two views, frontal and profile, should always be taken, before and after filling. Retrograde pyelography should always be employed; a catheter should be placed in the ureter to maintain its normal form without straightening out its pathologic curvatures.

INFECTION OF THE URINARY TRACT

Sewell, Kasper and Broom [80] reported a case in which the results of bacteriologic and histologic examinations of the kidney indicated that chromogenic acid-fast bacilli may be pathogenic for man and may be capable of causing changes in the tissues likely to be confused with those caused by infection by the tubercle bacilli. An error in diagnosis may result if such organisms are studied only by means of the direct

80. Sewell, George; Kasper, Joseph, and Broom, Norma: Chromogenic Acid-Fast Bacillus Infection of the Urinary Tract, J. Urol. **37**:385-393 (March) 1937.

smear or if reliance is placed on animal inoculation for the diagnosis. Pinner has demonstrated that inoculation of animals with chromogenic acid-fast bacilli will result in the development of lesions, which may disappear by the end of the period usually required for the development of tubercles.

Since the pathogenicity of some, at least, of the chromogenic acid-fast bacilli is established, caution should be exercised when reporting the results of direct microscopic examination of cystoscopic or simple catheterized specimens of urine. Otherwise, an erroneous diagnosis of tuberculosis might be the result.

The true nature of the chromogenic acid-fast bacilli has not yet been determined. Further work is now in progress to learn if they are related to tubercle bacilli. In a series of 130 specimens of sputum obtained from known tuberculous patients, 34 of which gave positive cultures, approximately 20 per cent were found to contain chromogenic organisms.

Although nephrectomy was performed for the complete relief of symptoms in the case which was reported, it is probable that in similar cases in which there is less extensive involvement of the urinary tract the patient may recover spontaneously. The animal experiments of Pinner and those in the authors' laboratory tend to support this view.

URINARY ANTISEPSIS

Cook [81] stated that the oral administration of synthetic racemic beta-hydroxybutyric acid causes definite increase in urinary excretion of this substance when the patient to whom the drug is given is in a state of sufficient ketosis. There is no change when the substance is given to a patient who displays little or no ketosis.

The local use of a 2 per cent solution of beta-hydroxybutyric acid buffered to a p_H of from 4.4 to 4.5 has proved beneficial in those cases in which the results with the diet have been unsuccessful or the patient has been unable to stand the dietary regimen. Seven of the ten patients so treated gave negative urinary cultures. In 2 of the remaining 3, symptoms were markedly relieved, while in 1 no benefit was obtained.

The sodium salt of beta-hydroxybutyric acid when given orally will produce an increase in urinary excretion of the acid, but apparently to a less degree than oral administration of the pure acid.

The calcium salt of beta-hydroxybutyric acid was given intravenously in 3 cases. In none of these was an appreciable change noted in the urinary concentration of the acid.

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81. Cook, E. N.: The Use of Beta Hydroxybutyric Acid and Certain of Its Salts as an Adjunct in the Treatment of Infections of the Urinary Tract, J. Urol. **36**:289-297 (Sept.) 1936.

Buchtel and Cook [82] reported that according to replies to questionnaires from 161 patients who had bacillary infections of the urinary tract and who had been treated by means of the ketogenic diet on an average of two years previously, 26 per cent had recurrences. There was little difference in the incidence of recurrence of the various bacilli. In the majority of cases the recurrence was mild and occurred within the first three months. A ketogenic diet suitable for use in the home was outlined. The ketogenic diet is a successful method of treatment, not only in regard to the immediate results but also in regard to end-results.

HYPERPYREXIA

Potter, Redewill and Longley [83] discussed various agents for producing therapeutic fever. Physical agents used for the production of therapeutic fever are of two classes: those operating in a medium higher than the body temperature and those operating in a medium lower than the body temperature. The former are not considered physiologically as desirable as the latter. The biophysical action of the latter, with which the heat is generated in the body, the lessened shock-producing elements involved, the added comfort of the patient and the consistently lower pulse rate that occurs when prolonged high temperatures are maintained by application of electromagnetic induction in the cool cabinet make their use the method of choice.

Hyperpyrexia may prove dangerous or fatal unless given by skilled operators, and the mismanagement in cases of emergencies has done much to bring it into disrepute.

One hundred and eighty-nine cases of gonorrheal infection and complications were reported; 1,001 hyperpyrexia treatments were given with the inductotherm and the Kimble cabinet. The results were most striking in cases of gonorrheal arthritis. However, all types of gonorrheal infection except chronic posterior urethritis responded satisfactorily to fever therapy. In the 1,001 treatments given with hyperpyrexia, only 3 serious reactions developed (heat collapse), and there were no fatalities.

Active chemotherapy in the form of intravenous injection of dextrose and mercurochrome seems to aid the therapeutic effect of hyperpyrexia.

The production of therapeutic fever with the electromagnetic induction in the Kimble cabinet has added greatly to the urologist's armamentarium.

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82. Buchtel, H. A., and Cook, E. N.: End-Results of Treatment of Urinary Infections by the Ketogenic Diet, Minnesota Med. **19**:603 (Sept.) 1936.

83. Potter, J. E.; Redewill, F. H., and Longley, E. G.: Hyperpyrexia as an Adjunct in Treatment of Non-Surgical Urological Conditions, J. Urol. **37**:214-225 (Jan.) 1937.